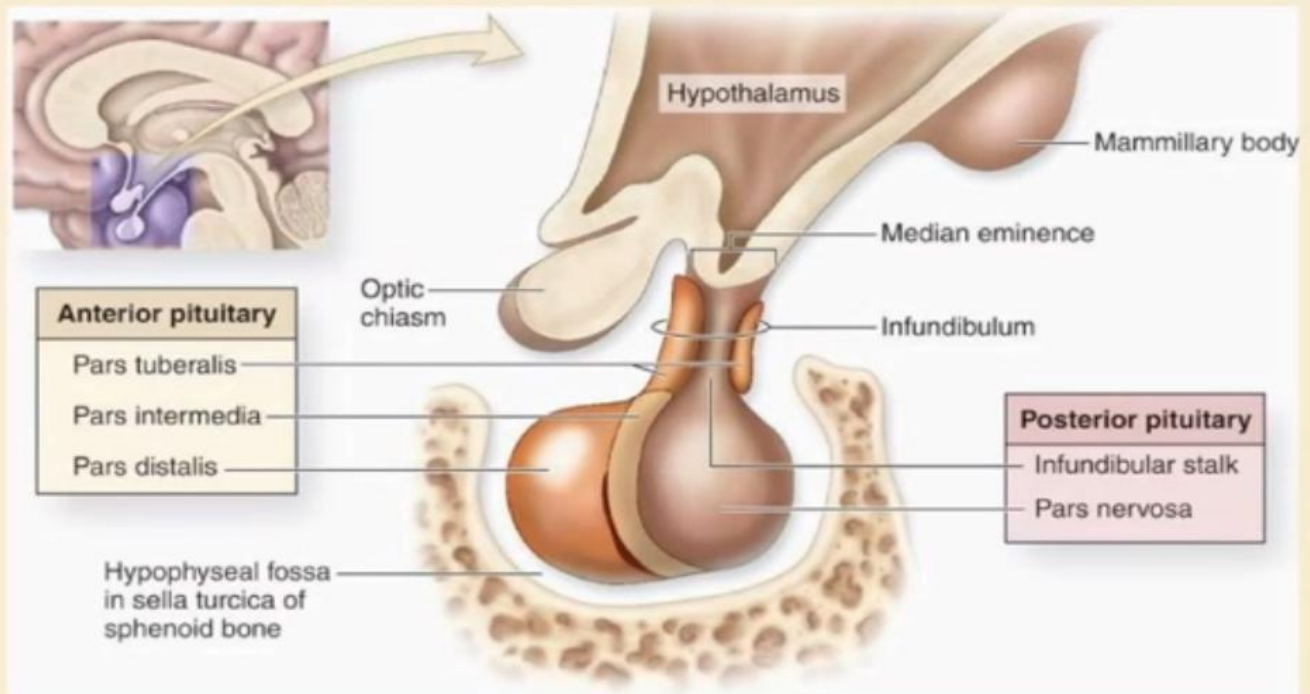


# Pituitary

## Overview of the Anterior Pituitary

- ◆ Secretes the hormones FSH, LH, ACTH, TSH, prolactin, and GH
- ◆ Stimulated to release hormones by the hypothalamus ("releasing hormones")

## Anatomy



## Anatomy



VISIT...

LANZAROTE  
*Caliente*.COM

## Diseases of the Anterior Pituitary

- ◆ Hyperprolactinemia
- ◆ Acromegaly
- ◆ Hypopituitarism
  - ◆ Pituitary apoplexy
  - ◆ Sheehan's syndrome
  - ◆ Stroke
  - ◆ Infiltration (TB, sarcoidosis, syphilis, hemochromatosis)
  - ◆ Autoimmune disease
  - ◆ Trauma
- ◆ Empty sella syndrome

### **Pituitary apoplexy:**

Sudden enlargement of pituitary tumour secondary to hemorrhage or infarction

#### **Features:**

- 1) sudden onset headache similar to that seen in subarachnoid hemorrhage
- 2) vomiting
- 3) neck stiffness
- 4) visual field defects: classically bitemporal superior quadrantic defect
- 5) extraocular nerve palsies
- 6) hypopituitarism e.g. Hypotension secondary to hypoadrenalism

### Dynamic pituitary function tests:

- A dynamic pituitary function test is used to assess patients with suspected primary pituitary dysfunction
- Insulin, TRH and LHRH are given to the patient following which the serum glucose, cortisol, growth hormone, TSH, LH and FSH levels are recorded at regular intervals. Prolactin levels are also sometimes measured\*

### **A normal dynamic pituitary function test has the following characteristics:**

- GH level rises  $> 20\text{mu/l}$
- cortisol level rises  $> 550\text{ mmol/l}$
- TSH level rises by  $> 2\text{ mu/l}$  from baseline level
- LH and FSH should double

### **Dopamine antagonist tests using metoclopramide may also be used in the investigation of hyperprolactinaemia:**

- A normal response is at least a two fold rise in prolactin.
- A blunted prolactin response suggests a prolactinoma

### Insulin stress test:

- used in investigation of hypopituitarism
- IV insulin given, ----->GH and cortisol levels measured
- with normal pituitary function GH and cortisol should rise

### **Contraindications:**

- 1) epilepsy (**use glucagon instead**)
- 2) ischaemic heart disease
- 3) adrenal insufficiency

# **Pituitary tumours**

## **Hormones secreted**

- Prolactin- 35%
- 'Non-functioning', 'chromophobe' - 30%, no obvious hormone
- GH - 20%
- Prolactin and GH - 7%
- ACTH - 7%
- Others: TSH, LH, FSH - 1%

## **Pregnancy** سؤال متكرر

TSH is often slightly decreased or low-normal, perhaps as a result of hCG.

Other hormonal changes that occur in normal pregnancy include;

- increased cortisol-binding globulin, increased free and total cortisol, and
- increased aldosterone, prolactin, oestrogen (which can lead to low LH and FSH) and progesterone

# Prolactin and galactorrhoea

- Prolactin is secreted by the anterior pituitary gland with release being controlled by a wide variety of physiological factors.
- **Dopamine** acts as the primary prolactin release inhibitory factor and hence dopamine agonists such as bromocriptine may be used to control galactorrhoea.
- It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia

## Features of excess prolactin: (prolactin inhibits FSH&LH)

- men: impotence, loss of libido, galactorrhoea
- women: amenorrhoea, galactorrhoea

## Causes of raised prolactin:

### 1) prolactinoma

- ⇒ in males it is macroadenoma so it cause bitemporal hemianopsia
- ⇒ in female it is microadenoma

### 2) pregnancy

### 3) oestrogens

### 4) physiological: stress, exercise, sleep, sex, suckling

### 5) polycystic ovarian syndrome PCO

### 6) acromegaly: 1/3 of patients with acromegaly has elevated prolactin

### 7) primary hypothyroidism ( thyrotrophin releasing hormone (TRH) stimulating prolactin release)

## Drug causes of raised prolactin: (dopamine antagonists and serotonin)

- metoclopramide, domperidone
- phenothiazines, haloperidol.
- very rare: SSRIs, opioids

## Prolactin inhibitors: dopamine

## Prolactin stimulants: TRH & serotonin

N.B. Stalk compression with a non-functioning tumour may cause hyperprolactinaemia (d.t. decreased delivery of dopamine to ant. Pituitary) but the concentrations of prolactin are usually below 2000 mU/L and **galactorrhoea would be rare.**

## Investigation:

### 1) Prolactin level:

- ☒ prolactin above 2000 mU/L is suggestive of a prolactinoma rather than a nonfunctioning tumour with stalk compression.

NB In polycystic ovarian syndrome: Prolactin level below 1000 mU/L

### 2) MRI

## Treatment:

Dopamine agonist ( **cabergoline**, **bromocriptine**)

# **Gynaecomastia**

- Abnormal amount of breast tissue in males and is usually caused by an increased oestrogen: androgen ratio.
- It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia

## **Causes of gynaecomastia:**

- 1) physiological: normal in puberty
- 2) syndromes with androgen deficiency: Kallman's, Klinefelter's
- 3) testicular failure: e.g. mumps
- 4) testicular cancer e.g. seminoma secreting HCG
- 5) ectopic tumour secretion
- 6) hyperthyroidism
- 7) liver disease
- 8) haemodialysis
- 9) drugs: see below

## **Drug causes of gynaecomastia:**

- 1) spironolactone (most common drug cause)
- 2) digoxin
- 3) cimetidine
- 4) cannabis
- 5) finasteride
- 6) gonadorelin analogues e.g. Goserelin, buserelin  
Goserelin is a gonadorelin analogue used in the treatment of advanced prostate cancer.
- 7) oestrogens, anabolic steroids

## **Very rare drug causes of gynaecomastia:**

- 1) tricyclics
- 2) isoniazid
- 3) calcium channel blockers
- 4) heroin
- 5) busulfan
- 6) methyldopa

The incidence of gynaecomastia typically occurs at three distinct periods of life:

- Neonatal - due to maternal oestrogens crossing the placenta
- Puberty - low testosterone and dihydrotestosterone (DHT) during puberty
- Adult life - typically 50-80-years-old, which may be due to primary testicular failure, obesity or alcohol excess.



The picture shows gynecomastia in a patient with a history suggesting Klinefelter's syndrome.

Klinefelter's is characterised by tall stature, small testes, azoospermia and gynecomastia in a male.

Plasma gonadotrophins are raised.

Typical karyotype is [47XXY](#), though mosaics occur with 46XY/47XXY karyotype. There is an increased risk of breast cancer (20 times higher than a normal male).



# **Growth hormone**

- Anabolic hormone secreted by the somatotroph cells of the anterior lobe of the pituitary gland.
- It has actions on multiple organ systems and is important in postnatal growth and development.
- GH is also responsible for changes in protein, lipid, and carbohydrate metabolism

## **Mechanism of action:**

- acts on a **transmembrane receptor** for growth
- binding of GH to the receptor leads to **receptor dimerization**
- acts **directly** on tissues and also **indirectly** via **insulin-like growth factor 1 (IGF-1)**, primarily secreted by the liver

## **GH release is increased by:**

- 1) Deep sleep
- 2) Fasting, Hypoglycaemia
- 3) Alpha adrenergic activity
- 4) Stress
- 5) Exercise
- 6) Sex steroids
- 7) Amino acids
- 8) Thyroxine, and
- 9) Ghrelin.

## **GH release is inhibited by:**

- 1) Somatostatin
- 2) IGF-1.
- 3) Cortisol
- 4) Beta adrenergic activity
- 5) Hyperglycaemia
- 6) Obesity
- 7) Free fatty acids
- 8) Hypothyroidism,

## **Conditions associated with GH disorders**

- excess GH: acromegaly
- GH deficiency: resulting in short stature

# **Growth hormone deficiency**

- Growth hormone deficiency is uncommon in children and in adults.

**In children**, short stature is often idiopathic and only around 8% of referred patients will have GH deficiency.

## **In adults**

- GH deficiency most commonly occurs after pituitary surgery or radiotherapy.
- It can be insidious in its presentation and may be asymptomatic.
- There is some evidence that it can cause altered body composition, which can be treated.
- Baum and colleagues (see below) found that adult patients with GH deficiency treated with recombinant GH had improved bone mineral density, reduced fat mass and increased lean tissue mass after 18 months.
- GH deficiency in adults has also been associated with premature mortality.

## **Diagnosis:**

- The diagnosis of GH deficiency often requires dynamic function testing.
- **The gold standard test** is the **insulin tolerance test**:
  - ⇒ Insulin is given to stimulate significant hypoglycaemia (glucose less than 2.2 mmol/L)
  - ⇒ This provokes GH and adrenocorticotrophic hormone (ACTH) release.
  - ⇒ Samples are taken at baseline and at 30, 60 and 90 minutes.
  - ⇒ A normal result is a rise in cortisol to more than 550 nmol/L and a rise in GH to more than 10 µg/L
  - ⇒ Patients with a history of seizures or heart disease are unsuitable for this test.
- A random growth hormone level must be interpreted with caution due to significant diurnal variation. A level of GH greater than 3 µg/L probably excludes GH deficiency
- Normal GH stimulates IGF-1 release and IGF-1 concentrations are often low in GH deficiency.

# Acromegaly

- There is excess growth hormone secondary to a **pituitary adenoma** in **> 95%** of cases.
- A minority of cases are caused by **ectopic GHRH** or **GH production** by tumours e.g. pancreatic .....acromegaly تخيل ممكن ورم بنكرياس يعمل

## Features:

- 1) coarse facial appearance, spade-like hands, increase in shoe size
- 2) large tongue, prognathism, interdental spaces
- 3) excessive sweating and oily skin
- 4) features of pituitary tumour: hypopituitarism, headaches, bitemporal hemianopia
- 5) raised prolactin in 1/3 of cases → galactorrhoea
- 6) 6% of patients have MEN-1 (70% of MEN1 have Acromegaly)

## Complications:

- HTN, Cardiomyopathy
- DM (>10%) - colorectal cancer

## Investigations:

Growth hormone (GH) levels vary during the day and are therefore not diagnostic

- 1) The definitive test is **Oral glucose tolerance (OGTT)** with **serial GH measurements**.
- 2) **Serum IGF-1** may also be used as a **screening test** and is sometimes used to **monitor disease**
- 3) **A pituitary MRI** may demonstrate a pituitary tumour

## Oral glucose tolerance test with serial GH measurements

- in normal patients GH is suppressed to  $< 2 \mu\text{u/L}$  with hyperglycaemia
- in acromegaly there is no suppression of GH
- may also demonstrate impaired glucose tolerance which is associated with acromegaly

## Management:

- 1) **Trans-sphenoidal surgery** is **first-line treatment** for acromegaly in the majority of patients
- 2) **Somatostatin analogue: (Octreotide)**
  - ☒ effective in 50-70% of patients
  - ☒ may be used as an adjunct to surgery
- 3) **GH receptor antagonist: (Pegvisomant)**
  - prevents dimerization of the GH receptor
  - once daily s/c administration
  - very effective - decreases IGF-1 levels in 90% of patients to normal
  - doesn't reduce tumour volume therefore surgery still needed if mass effect
- 4) **Dopamine agonists: (Bromocriptine)**
  - ☒ The first effective medical treatment for acromegaly, however now superseded by somatostatin analogues.
  - ☒ Effective only in a minority of patients.

- 5) External irradiation is sometimes used for older patients or following failed surgical/medical treatment



This patient appears acromegalic

## Hypopituitarism

- ◆ Causes
  - ◆ **Pituitary apoplexy:** Hemorrhage into the pituitary, generally secondary to an adenoma. Acute sx of headache, nausea, vomiting, AMS, low BP, low blood sugar
  - ◆ **Sheehan's syndrome:** Ischemic necrosis of pituitary postpartum. Usually noted by difficulty breastfeeding. Extended amenorrhea.
  - ◆ **Infiltration** (sarcoidosis, hemochromatosis, TB, syphilis)
  - ◆ **Non-functioning adenoma**
  - ◆ **Trauma**
  - ◆ **Stroke**
  - ◆ **Mass effect**

## How are hormones measured?

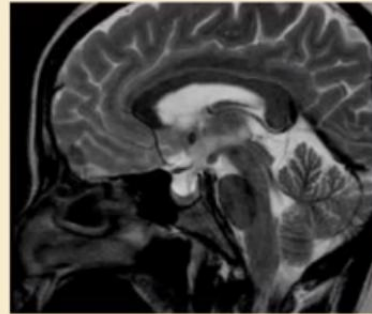
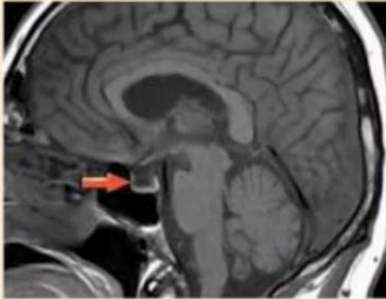
- ◆ **LH/FSH:** Directly
- ◆ **GH:** Indirectly via IGF-1, or directly via GH insulin response test
  - ◆ Administer 0.1µg/kg insulin, or until blood glucose is 40mg/dL. Low blood glucose should stimulate GH release. If GH is < 10 mg/L, it is low.
- ◆ **TSH:** Directly via TSH, T3, T4
- ◆ **ACTH:** Indirectly via cortisol

- ◆ **Sx:** In general, LH/FSH → GH → TSH → ACTH.
  - ◆ **Decreased LH/FSH:** Amenorrhea, infertility, decreased pubic and axillary hair, genital atrophy, decreased libido, erectile dysfunction
  - ◆ **Decreased GH:** Clinically undetectable
  - ◆ **Decreased TSH:** Fatigue, weight gain, weakness, decreased appetite, cold intolerance
  - ◆ **Decreased ACTH:** Fatigue, decreased appetite, decreased pigmentation, low BP, low glucose
- ◆ **Dx:** The best initial test is to measure levels of AP hormones. MRI must be performed, either to confirm pituitary apoplexy or to exclude adenoma.

- ◆ **Tx:** Treatment of underlying cause and hormone replacement.
- ◆ For pituitary apoplexy, surgical decompression is needed.

## Empty Sella Syndrome

- Usually an incidental finding
- Typical presentation: Headache and hypertension in an obese woman
- No therapy needed



Normal 😊



# **Posterior Pituitary**

## **Antidiuretic hormone**

- Antidiuretic hormone (ADH) is secreted from the posterior pituitary gland.
- It promotes water reabsorption in collecting ducts of the kidneys by the insertion of aquaporin-2 channels

## **Diabetes insipidus**

A condition characterised by either a deficiency of antidiuretic hormone (cranial DI) or insensitivity to antidiuretic hormone (nephrogenic DI)

### **Causes of cranial DI:**

- 1) idiopathic
- 2) post head injury
- 3) pituitary surgery
- 4) craniopharyngiomas
- 5) histiocytosis X
- 6) **DIDMOAD** is the association of cranial Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness (also known as Wolfram's syndrome)

### **Causes of nephrogenic DI:**

- 1) **Genetic:**
  - ☒ The more common form affects the vasopressin (ADH) receptor,
  - ☒ The less common form results from a mutation in the gene that encodes the aquaporin 2 channel
- 2) **Electrolytes:** **hypercalcaemia, hypokalaemia**
- 3) **Drugs:**
  - ☒ demeclocycline,
  - ☒ lithium
- 4) **Tubulo-interstitial disease:**
  - ☒ obstruction,
  - ☒ pyelonephritis
  - ☒ sickle-cell,

**Features:** **polyuria, polydipsia**

### **Investigation:**

- 1) **high plasma osmolality, low urine osmolality**
  - ☒ plasma osmolality >305mOsm/kg
  - ☒ serum [Na] >145 mmol/L, and
  - ☒ urine osmolality <200 mOsm/kg
  - ☒ urinary [Na] 20-60 mmol/L
  - ☒ Urinary specific gravity <1.005.
- 2) **water deprivation test**

### **Treatment:**

- 1) **Increase oral water intake.** In the unconscious patient, nasogastric water and/or intravenous 5% dextrose can be administered.
- 2) **Synthetic ADH** can be given intranasally or intravenously if the urine output continues to be greater than 250 ml/hr.

### Cerebral salt wasting syndrome

- causes polyuria and dehydration secondary to urinary sodium losses,
- But it is characterized by hyponatraemia and a serum osmolality < 280 mOsm/kg

Furosemide-induced diuresis is associated with a serum [sodium] <135 mmol/L and a serum osmolality <280 mOsmol/kg.

### Water deprivation test:

- prevent patient drinking water
- ask patient to empty bladder
- hourly urine and plasma osmolalities

|                        | Starting plasma osm | Final urine osm. | Urine osm. post-DDAVP |
|------------------------|---------------------|------------------|-----------------------|
| Normal                 | Normal              | > 600            | > 600                 |
| Psychogenic polydipsia | Low                 | > 400            | > 400                 |
| Cranial DI             | High                | < 300            | > 600                 |
| Nephrogenic DI         | High                | < 300            | < 300                 |



# **SIADH**

- ADH is released at a plasma osmolality  $> 280$  mosmol/kg: this is called the osmotic threshold.
- The syndrome of inappropriate ADH secretion is characterised by hyponatraemia secondary to the dilutional effects of excessive water retention.

## **Causes:**

| Category     | Examples                                                                                                                                                             |
|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Malignancy   | <ul style="list-style-type: none"><li>• small cell lung cancer</li><li>• also: pancreas, prostate</li></ul>                                                          |
| Neurological | <ul style="list-style-type: none"><li>• stroke</li><li>• subarachnoid haemorrhage</li><li>• subdural haemorrhage</li><li>• meningitis/encephalitis/abscess</li></ul> |
| Infections   | <ul style="list-style-type: none"><li>• tuberculosis</li><li>• pneumonia</li></ul>                                                                                   |
| Drugs        | <ul style="list-style-type: none"><li>• sulfonylureas</li><li>• SSRIs, tricyclics</li><li>• carbamazepine</li><li>• vincristine</li><li>• Cyclophosphamide</li></ul> |
| Other causes | <ul style="list-style-type: none"><li>• positive end-expiratory pressure (PEEP)</li><li>• porphyrias</li></ul>                                                       |

## **The diagnosis of SIADH requires;**

- 1) the patient to be euvolaemic with
- 2) low serum sodium or osmolality ( $<134$  mmol/l or  $<280$  mosmol/kg respectively) with
- 3) An inappropriately high urine sodium and osmolality ( $>40$  mmol/l;  $>100$  mosmol/kg),
- 4) with exclusion of other causes such as glucocorticoid deficiency, hypothyroidism and diuretic therapy.

## **Management:**

- 1) Correction of hyponatremia must be done **slowly** (0.5-1.0 mmol/hour) to avoid precipitating **central pontine myelinolysis**
- 2) **Fluid restriction**
- 3) **Demeclocycline**: reduces the responsiveness of the collecting tubule cells to ADH
- 4) **ADH (vasopressin) receptor antagonists** (tolvaptan) reserved for more refractory cases.

# **Amenorrhea**

Amenorrhea may be divided into:

- A) **Primary** (failure to start menses by the age of 16 years) or
- B) **Secondary** (cessation of established, regular menstruation for 6 months or longer)

## **Causes of primary amenorrhea:**

- 1) Turner's syndrome
- 2) Androgen insensitivity syndrome (testicular feminization TFS)
- 3) congenital adrenal hyperplasia CAH
- 4) congenital malformations of the genital tract

## **Causes of secondary amenorrhea (after excluding pregnancy)**

- 1) hypothalamic amenorrhea (e.g. Stress, excessive exercise)
- 2) hyperprolactinaemia
- 3) thyrotoxicosis\*
- 4) polycystic ovarian syndrome (PCOS)
- 5) premature ovarian failure

\*hypothyroidism may also cause amenorrhea

## **Initial investigations**

- 1) exclude pregnancy with urinary or serum b-HCG
- 2) gonadotrophins:
  - ⇒ low levels indicate a hypothalamic cause
  - ⇒ raised levels suggest an ovarian problem (e.g. Premature ovarian failure)
- 3) prolactin
- 4) thyroid function tests
- 5) androgen levels: raised levels may be seen in PCOS
- 6) oestradiol

# **Premature ovarian failure**

Defined as the onset of menopausal symptoms and elevated gonadotrophin levels (LH & FSH) before the age of 40 years

## **Causes:**

- 1) idiopathic - the most common cause
- 2) autoimmune
- 3) chemotherapy
- 4) radiation

**Features** are similar to those of the normal climacteric but the actual presenting problem may differ

- 1) climacteric symptoms: hot flushes, night sweats
- 2) infertility
- 3) secondary amenorrhoea
- 4) raised FSH, LH levels

# Polycystic ovarian syndrome

- Polycystic ovary syndrome (PCOS) is a complex condition of ovarian dysfunction
- affect between 5-20% of women of reproductive age
- The aetiology of PCOS is not fully understood.
- Both **hyperinsulinaemia** and high levels of **LH** are seen in PCOS and there appears to be some overlap with the metabolic syndrome.

## Features:

- 1) Subfertility and infertility.
- 2) Menstrual disturbances: oligomenorrhea and amenorrhoea.
- 3) Hirsutism, acne (due to hyperandrogenism).
- 4) Obesity.
- 5) Acanthosis nigricans (due to insulin resistance).

## Investigations:

- 1) pelvic ultrasound: multiple cysts on the ovaries
- 2) FSH, LH, prolactin, TSH, and testosterone are useful investigations:
  - ☒ Raised LH: FSH ratio:  
A 'classical' feature but is no longer thought to be useful in diagnosis
  - ☒ Prolactin may be normal or mildly elevated not exceeding 1000 mU/L.
  - ☒ Testosterone may be normal or mildly elevated - however, if markedly raised consider other causes
- 3) check for impaired glucose tolerance

## Management:

- Management is complicated because the aetiology of PCOS is not fully understood.
- 1) General:
    - weight reduction if appropriate
    - if a women requires contraception then a combined oral contraceptive (**COC**) pill may help regulate her cycle and induce a monthly bleed (see below)
  - 2) Hirsutism and acne:
    - ☒ **A COC pill** may be used help manage hirsutism.  
Possible options include:
      - 1) **a third generation COC** which has fewer androgenic effects or
      - 2) **Co-cyprindiol** which has an anti-androgen action.Both of these types of COC may carry an **increased risk of venous thromboembolism**
    - ☒ if doesn't respond to COC then **topical eflornithine** may be tried
    - ☒ **spironolactone**, **flutamide** and **finasteride** may be used under specialist supervision

### 3) Infertility:

- weight reduction if appropriate
- The management of infertility in patients with PCOS should be supervised by a specialist.
- There is an ongoing debate as to whether metformin, clomifene or a combination should be used to stimulate ovulation.

#### A) Clomifene:

- ☒ Work by occupying hypothalamic oestrogen receptors without activating them. This interferes with the binding of oestradiol and thus prevents negative feedback inhibition of FSH secretion
- ☒ A 2007 trial published in the NEJM suggested clomifene was the most effective treatment.
- ☒ There is a **potential risk of multiple pregnancies** with anti-oestrogen therapies such as clomifene.

#### B) Metformin:

- ☒ The RCOG published an opinion paper in 2008 and concluded that on current evidence metformin is not a first line treatment of choice in the management of PCOS
- ☒ metformin is also used, either combined with clomifene or alone, particularly in patients who are obese

#### C) Gonadotrophins

# **Androgen insensitivity syndrome**

- Androgen insensitivity syndrome is an X-linked recessive condition due to end-organ resistance to testosterone causing genotypically male children (46XY) to have a female phenotype.
- Complete androgen insensitivity syndrome is the new term for **testicular feminisation syndrome**

## **Features:**

- 1) primary amenorrhoea
- 2) undescended testes causing groin swellings
- 3) breast development may occur as a result of conversion of testosterone to oestradiol

## **Diagnosis:**

- buccal smear or chromosomal analysis to reveal 46XY genotype

## **Management:**

- 1) counselling - raise child as female
- 2) bilateral orchidectomy (increased risk of testicular cancer due to undescended testes)
- 3) oestrogen therapy

تربيته بنت..... وتشيل الخصيتين.....وتديها استروجين.....

A 32 year old female presents to the infertility clinic with an inability to conceive. She is overweight, with a body mass index of 32 kg/m<sup>2</sup>, and has noticed increased hair growth over her face and chest over the last 12 months. Her periods are irregular and she has also noticed a deepening of her voice. An ultrasound of the pelvis has revealed the presence of multiple cysts in both ovaries. She has been treated with cyproterone acetate for her hirsutism but was informed that she should not attempt conception whilst on the drug. She now wishes to conceive.

On examination she has a cushingoid appearance, with abdominal striae and her blood pressure is 140/85 mmHg.

Laboratory investigations reveal:

|                           |                                     |
|---------------------------|-------------------------------------|
| <b>9:00 am Cortisol</b>   | <b>710 nmol/l (170- 700 nmol/l)</b> |
| <b>LH</b>                 | <b>28 iU/l (1-20 iU/l)</b>          |
| <b>Basal FSH</b>          | <b>4.7 iU/l (1.0 - 8.8 iU/l)</b>    |
| <b>DHEAS</b>              | <b>509 µg/dl (31- 228 µg/dl)</b>    |
| <b>Prolactin</b>          | <b>602 mU/l (&lt;360 mU/l)</b>      |
| <b>17 OH Progesterone</b> | <b>54 ng/dl (&lt;80 ng/dl)</b>      |

Which of the following treatment options would be most appropriate for the treatment of infertility?

|                                      |
|--------------------------------------|
| a) Metformin                         |
| b) Spironolactone                    |
| c) Reverse circadian rhythm steroids |
| d) Clomiphene citrate                |
| e) Cabergoline                       |

**The Rotterdam criteria for the diagnosis of PCOS** requires at least two of the following

- Clinical or biochemical evidence of hyperandrogenism.
- Evidence of oligo- or anovulation.
- Presence of polycystic ovaries on ultrasound.

Multiple clinical trials have been conducted to assess which drug is the most appropriate in aiding fertility. An article published in the New England journal of Medicine entitled Clomiphene, Metformin, or Both for Infertility in the Polycystic Ovary Syndrome concluded that Clomiphene is superior to metformin in achieving live birth in infertile women with the polycystic ovary syndrome, although multiple birth is a complication(N Engl J Med 2007; 356:551-566 February 8, 2007).

Another article Status of clomiphene citrate and metformin for infertility in PCOS (Trends Endocrinol Metab. 2012 Oct;23(10):533-43) published the following results: 'Though widely used, there is uncertainty about the effectiveness and adverse effects of metformin and clomiphene citrate (CC) for infertility in polycystic ovary syndrome (PCOS). A systematic review (SR) of the best available evidence suggests that both CC and metformin are better than placebo for increasing ovulation and pregnancy rates, but CC is more effective than metformin for ovulation, pregnancy and live-birth rates, in PCOS patients with body mass index (BMI) >30.'

In PCOS, serum prolactin may also be marginally raised, but the levels seldom exceed 1500 mU/l.

Reverse circadian rhythm steroids are used in the treatment of congenital adrenal hyperplasia, whilst cabergoline is used for the medical management of hyperprolactinemia.

Spironolactone has antiandrogenic activity and can cause improvements in hirsutism in PCOS but has no bearing on fertility.

A 42-year-old woman was seen in Endocrinology Clinic with a 4 month history of amenorrhoea. On questioning she reports having to wax her arms and upper lip. Her mother went through early menopause at 28 after having an emergency hysterectomy post-partum. On examination her BMI is 38 but otherwise unremarkable.

Her GP has kindly ordered blood tests prior to her appointment

#### Investigations

|                                    |                                   |
|------------------------------------|-----------------------------------|
| <b>LH</b>                          | <b>40 IU/L (5 to 25 IU/L)</b>     |
| <b>FSH</b>                         | <b>8 IU/ (1 to 11 IU/L)</b>       |
| <b>Estradiol</b>                   | <b>720 pmol/L (70-500 pmol/L)</b> |
| <b>Progesterone</b>                | <b>220 nmol/L (35-92 nmol/L)</b>  |
| <b>Thyroid Stimulating Hormone</b> | <b>5.6 mIU/L (0.5 -6.0 mIU/L)</b> |
| <b>Prolactin</b>                   | <b>700 mIU/L (105-548mIU/L)</b>   |

What is the most likely diagnosis?

|                       |                             |
|-----------------------|-----------------------------|
| <input type="radio"/> | Prolactinoma                |
| <input type="radio"/> | Polycystic Ovarian Syndrome |
| <input type="radio"/> | Premature Ovarian Failure   |
| <input type="radio"/> | Pregnancy                   |
| <input type="radio"/> | Subclinical Hypothyroidism  |

The most likely diagnosis is pregnancy. The elevated estradiol and progesterone is characteristic with a slight rise in the LH level.

The prolactin level is only mildly elevated so a prolactinoma is unlikely especially with the rise in other hormone levels. Polycystic ovarian syndrome is associated with androgen excess and an elevated LH to FSH ratio. While androgen (testosterone) has not been measured, it is not associated with rises in estradiol or progesterone.

Premature Ovarian Failure typically presents with low levels of estradiol and a raised FSH level. Subclinical Hypothyroidism is linked with oligoovulation but in this case the TSH level is normal excluding this as a diagnosis

**Answer D**



# **Hypogonadism**

## **Primary hypogonadism:**

- The serum testosterone concentration and the sperm count are below normal and
- The serum LH and FSH concentrations are above normal.
- **Ultrasonic evaluation of the testes is the most appropriate investigation** if Testicular tumour, infiltration is suspected
- Although many testicular diseases damage both the seminiferous tubules and the Leydig cells, they usually damage the seminiferous tubules to a greater degree.
- As a consequence, the sperm count may be low, and the serum FSH concentration normal or high, yet the serum testosterone concentration remains normal.
- Haemochromatosis usually causes pituitary dysfunction

## **Secondary hypogonadism:**

- There is a proportionate reduction in testosterone and sperm production.
- The S. LH and FSH concentrations are normal or reduced.

## **Causes of primary hypogonadism in males:**

Can include congenital abnormalities and acquired diseases.

## **Congenital abnormalities:**

- Klinefelter syndrome (and other chromosomal abnormalities)
- Myotonic dystrophy.
- Mutation in the FSH and LH receptor genes
- Cryptorchidism
- Varicocele
- Disorders of androgen synthesis

## **Acquired diseases:**

- Infections (especially mumps)
- Radiation
- Trauma
- Testicular torsion
- Alkylating agents
- Ketoconazole, Glucocorticoids, Environmental toxins
- Autoimmune damage
- Chronic systemic illnesses
- Hepatic cirrhosis, Chronic renal failure
- AIDS
- Idiopathic.

# **Physiological changes in Pregnancy**

## **Progesterone:**

- during the first 2 weeks stimulates the fallopian tubes to secrete the nutrients the zygote/blastocyst requires
- placenta starts production at 6 weeks and takes over at 12 weeks
- progesterone inhibits uterine contractions by
  - 1) Inhibiting production of prostaglandins
  - 2) Decreasing sensitivity to oxytocin
- stimulates development of breast lobules and alveoli

## **Oestrogen:**

- oestriol is major oestrogen (not oestradiol)
- stimulates the continued growth of the myometrium
- stimulates the growth of the ductal system of the breasts

## **Prolactin:**

- increase during pregnancy probably due to oestrogen rise
- initiates and maintains milk secretion of the mammary gland
- essential for the expression of the mammatropic effects of oestrogen and progesterone
- oestrogen and progesterone directly antagonises the stimulating effects of prolactin on milk synthesis

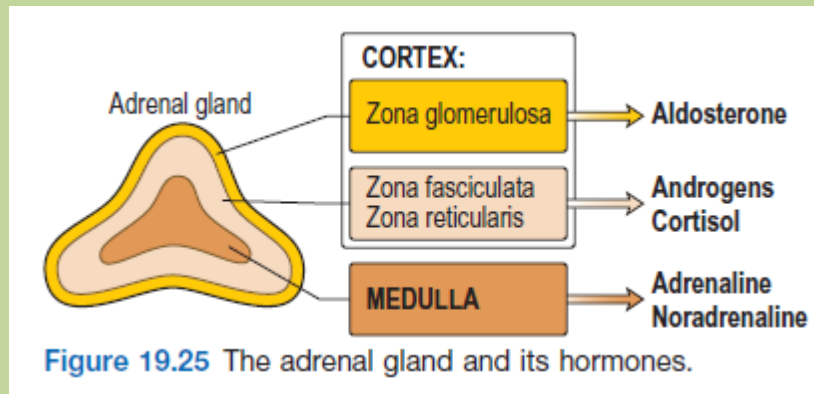
## **hCG:**

- secreted by syncytiotrophoblast, stimulated by GnRH produced in adjacent cytotrophoblast
- can be detected within 9 days, peak secretion at 9 weeks
- mimics LH, thus rescuing the corpus luteum from degenerating and ensuring early oestrogen and progesterone secretion
- stimulates production of relaxin
- may inhibit contractions induced by oxytocin

## **Also**

- Relaxin: suppresses myometrial contractions and relaxes the pelvic ligaments and pubic symphysis
- hPL: has lactogenic actions (insignificant with respect to prolactin) - antagonises insulin, therefore making less glucose available to the mother - enhances protein metabolism

# The Adrenal Gland



## **Adrenal cortex** (mnemonic GFR - ACD)

- zona glomerulosa (on outside): mineralocorticoids, mainly aldosterone
- zona fasciculata (middle): glucocorticoids, mainly cortisol
- zona reticularis (on inside): androgens, mainly dehydroepiandrosterone (DHEA)

# **Congenital Adrenal Hyperplasia**

- group of **autosomal recessive** disorders
- Caused by an inherited defect in the cortisol and/or aldosterone biosynthetic pathways.
- in response to resultant low cortisol levels the anterior pituitary secretes high levels of **ACTH**
- ACTH stimulates the production of **adrenal androgens** that may **virilize a female** infant
- The most common form is due to **21-hydroxylase deficiency**, but it can also result from 11 beta hydroxylase deficiency.
- **Non-classical forms:**
  - Result from milder enzyme dysfunction and therefore manifest later in life (adolescence or adulthood).
  - The clinical presentation may be indistinguishable from polycystic ovarian syndrome, with hirsutism being a dominant feature.

## **Cause:**

- ☒ **21-hydroxylase deficiency (90%)**
- ☒ **11-beta** hydroxylase deficiency (5%) → HTN with Hypokalemia
- ☒ **17-alpha** hydroxylase deficiency (very rare)

## **Clinical features:**

- **If severe**, CAH presents at birth with:
  - ☒ sexual ambiguity or
  - ☒ adrenal failure (collapse, hypotension, **hypoglycaemia**),
  - ☒ Sometimes with a salt-losing state (hypotension, hyponatraemia).
- **In the female:**
  - ☒ clitoral hypertrophy,
  - ☒ urogenital abnormalities and
  - ☒ labioscrotal fusion are common
- the syndrome may be unrecognized in **the male**
- **Rare milder cases**
  - ☒ Present in adult life, usually accompanied by primary amenorrhoea (may be 2ry).
  - ☒ Precocious puberty with hirsutism
  - ☒ Hirsutism developing before puberty is suggestive of CAH.

### **21-hydroxylase deficiency features:**

- **virilisation** of female genitalia
- **precocious puberty** in males
- 60-70% of patients have a **salt-losing crisis** at 1-3 wks of age

### **11-beta hydroxylase deficiency features:**

- **virilisation** of female genitalia
- **precocious puberty** in males
- **hypertension / hypokalaemia**

### **17-hydroxylase deficiency features:**

- **non-virilising** in females
- **inter-sex** in boys
- **hypertension**

### **Investigations:**

- 1) **Expert advice is essential** in the confirmation and differential diagnosis of 21-hydroxylase deficiency and with ambiguous genitalia such advice must be sought urgently before any assignment of gender is made.
- 2) **A profile of adrenocortical hormones** is measured before and 1 hour after ACTH administration.
  - ☒ 17-Hydroxyprogesterone levels are increased
  - ☒ Urinary pregnanetriol excretion is increased
  - ☒ Androstenedione levels are raised
  - ☒ Basal ACTH levels are raised.

### **Treatment:**

#### **Reverse circadian rhythm steroids:**

- Glucocorticoid activity must be replaced, as must mineralocorticoid activity if deficient.
  - In CAH the larger dose of glucocorticoid is often given at night to suppress the morning ACTH peak with a smaller dose in the morning.
  - Correct dosage is often difficult to establish in the child but should ensure normal 17-hydroxyprogesterone levels while allowing normal growth; excessive replacement leads to stunting of growth.
  - In adults, clinical features and biochemistry (plasma renin, androstenedione and 17-OH-progesterone) are used to modify treatment.
  - Genetic counselling and antenatal diagnosis is essential, particularly in 21-hydroxylase deficiency.
  - The mother of an affected fetus can take dexamethasone daily to prevent virilization.
- 
- ☒ 11 Beta-hydroxylase is responsible for conversion of 11-deoxycorticosterone and 11-deoxycortisol to corticosterone and cortisol.
  - ☒ In patients with 11-beta hydroxylase deficiency, levels of these steroids accumulate.
  - ☒ Whilst levels of 17-OH steroids are elevated in those with 11-beta hydroxylase deficiency, the elevation seen is not as great as that seen with 21-hydroxylase deficiency; occasionally an incorrect diagnosis of 21-hydroxylase deficiency may be made.

A 23 year old female presents with worsening acne and a marked increase in the development of body and facial hair which she finds very distressing. She is also overweight and is markedly stressed by her physical appearance and the development of stretch marks over her abdomen. She has tried multiple hair removal techniques with only mild success. On examination she has a body mass index of 28 kg/m<sup>2</sup>, coarse hair over the anterior and posterior part of her chest and under her chin. Her Blood Pressure is 135/90mmHg. Her lab results are as follows:

|                    |                             |
|--------------------|-----------------------------|
| 9:00 am Cortisol   | 345 nmol/l (170 700 nmol/l) |
| LH                 | 17 iU/l (1 20 iU/l)         |
| Basal FSH          | 7.1 iU/l (1.0 8.8 iU/l)     |
| DHEAS              | 545 µg/dl (31 228 µg/dl)    |
| Prolactin          | 160 mU/l (<360 mU/l)        |
| 17 OH Progesterone | 1025 ng/dl (<80 ng/dl)      |
| Testosterone       | 3.9 nmol/l (0.9 3.1 nmol/l) |

Ultrasound abdomen and pelvis reveals two cysts in the right ovary.

Which of the following is the most appropriate treatment option for her condition?

Combined oral contraceptive pill

Finasteride

Surgical resection of the ovarian cysts

Reverse circadian rhythm steroids

Metformin in combination with spironolactone

The diagnosis in this scenario is non-classical **congenital adrenal hyperplasia** which manifests in adolescence/adulthood. It is caused by deficiency in the enzyme 21 hydroxylase in the steroid biosynthetic pathway. The result is a shift in the production of steroid hormones towards the androgenic pathway. Since cortisol secretion is reduced, feedback leads to increased ACTH production and resultant hyperplasia of the adrenals. The level of the compounds that are formed prior to the action of 21 hydroxylase is increased, therefore levels of 17 hydroxyprogesterone are elevated. Due to excessive androgen production, there is virilization and hirsutism.

**Treatment** involves steroids given in reverse circadian rhythm, i.e. a higher dosage at night and a lower dose in the morning.

The rationale behind this approach is due to the pathophysiology of CAH. The adrenal hyperplasia and the over-secretion of adrenal androgens are due to excessive ACTH production. When steroids are given in higher doses at night, ACTH is suppressed and the normal physiological steroid peak in the morning is also reduced.

Cysts in the ovaries are a common finding on routine ultrasound and do not necessarily represent polycystic ovarian syndrome.

**Answer D**



## 20.30 Causes of hirsutism

| Cause                                                                    | Clinical features                                                                                                               | Investigation findings                                                                                                             | Treatment                                                                                   |
|--------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| <b>Idiopathic</b>                                                        | Often familial<br>Mediterranean or Asian background                                                                             | Normal                                                                                                                             | Cosmetic measures<br>Anti-androgens                                                         |
| <b>Polycystic ovarian syndrome</b>                                       | Obesity<br>Oligomenorrhoea or secondary amenorrhoea<br>Infertility                                                              | LH:FSH ratio > 2.5:1<br>Minor elevation of androgens*<br>Mild hyperprolactinaemia                                                  | Weight loss<br>Cosmetic measures<br>Anti-androgens<br>(Metformin, glitazones may be useful) |
| <b>Congenital adrenal hyperplasia</b><br>(95% 21-hydroxylase deficiency) | Pigmentation<br>History of salt-wasting in childhood, ambiguous genitalia, or adrenal crisis when stressed<br>Jewish background | Elevated androgens* which suppress with dexamethasone<br>Abnormal rise in 17OH-progesterone with ACTH                              | Glucocorticoid replacement administered in reverse rhythm to suppress early morning ACTH    |
| <b>Exogenous androgen administration</b>                                 | Athletes<br>Virilisation                                                                                                        | Low LH and FSH<br>Analysis of urinary androgens may detect drug of misuse                                                          | Stop steroid misuse                                                                         |
| <b>Androgen-secreting tumour of ovary or adrenal cortex</b>              | Rapid onset<br>Virilisation: clitoromegaly, deep voice, balding, breast atrophy                                                 | High androgens* which do not suppress with dexamethasone or oestrogen<br>Low LH and FSH<br>CT or MRI usually demonstrates a tumour | Surgical excision                                                                           |
| <b>Cushing's syndrome</b>                                                | Clinical features of Cushing's syndrome (p. 773)                                                                                | Normal or mild elevation of adrenal androgens*<br>See investigations (p. 774)                                                      | Treat the cause (p. 775)                                                                    |

\*e.g. Serum testosterone levels in women: < 2 nmol/L (< 58 ng/dL) is normal; 2–5 nmol/L (58–144 ng/dL) is minor elevation; > 5 nmol/L (> 144 ng/dL) is high and requires further investigation.

# Addison's disease

- **Autoimmune destruction** of the adrenal glands
- It is the commonest cause of hypoadrenalism in the UK, accounting for 80% of cases
- associated with other endocrine deficiencies in 10% of patients (autoimmune polyendocrinopathy syndrome APS)

## Other causes of hypoadrenalism:

### A) Primary causes:

- 1) tuberculosis
- 2) meningococcal septicaemia (Waterhouse-Friderichsen syndrome)
- 3) HIV
- 4) metastases (e.g. bronchial carcinoma)
- 5) antiphospholipid syndrome

### B) Secondary causes:

- 1) pituitary disorders (e.g. tumours, irradiation, infiltration)
- 2) Exogenous glucocorticoid therapy.

## Features of Addison's disease:

- 1) lethargy, **weakness**, postural hypotension
- 2) anorexia, nausea & vomiting,
- 3) **weight loss**
- 4) hyperpigmentation (especially palmar creases) {**ACTH stimulates secretion of melanocyte stimulating hormone in pars intermedia**}
- 5) vitiligo,
- 6) loss of pubic hair & loss of libido in women
- 7) crisis: collapse, shock, pyrexia
- 8) **eosinophilia**
- 9) electrolyte abnormalities:
  - hyponatraemia, hyperkalaemia & metabolic acidosis
  - hypoglycaemia
  - low aldosterone
  - elevated TSH and mild hypercalcaemia

- Dehydroepiandrosterone DHEA is the most abundant circulating adrenal steroid.
- Adrenal glands are the main source of DHEA in females
- Loss of functioning adrenal tissue as in Addison's disease may result in symptoms secondary to androgen deficiency, such as loss of libido.
- Research is ongoing as to whether routine replacement of DHEA is beneficial

## Addison's disease investigations:

- 1) **The definite investigation** is ACTH stimulation test (**short Synacthen test**). Plasma cortisol is measured before and 30 minutes after giving Synacthen 250 ug IM.
- 2) **Adrenal autoantibodies** such as **anti-21-hydroxylase** may also be demonstrated



**Addison's disease (primary hypoadrenalism) is associated with:**

- Low aldosterone secretion (leading to salt wasting)
- High plasma renin
- Elevated plasma vasopressin, and Angiotensin II.
- High adrenocorticotrophic hormone (ACTH)
- High lipotropin



Buccal pigmentation in Addison's disease is shown.

This 41-year-old female presents with weight loss, weakness, increased tanning (during winter) and dizziness on standing.

Which of the following antibodies would provide diagnostic information?

- a) Anti-endomysial antibodies
- b) Anti-glutamic acid decarboxylase antibodies
- c) Anti-intrinsic factor antibodies
- d) Anti-thyroid peroxidase antibodies
- e) Anti-21 hydroxylase antibodies

This patient's symptoms are classical for Addison's disease. Increased tanning during winter is particularly suggestive and due to the action of excess ACTH on melanocytes. The tanned and thin appearance is demonstrated in the photograph. Anti-21 hydroxylase antibodies are typically seen in a high percentage (80-90%) of such cases.

Although other antibodies may be present, they are not as frequent.

**Answer E**

# **Primary hyperaldosteronism**

- **Bilateral idiopathic adrenal hyperplasia** 70% of cases.
- Primary hyperaldosteronism was previously thought to be most commonly caused by an **adrenal adenoma**, termed **Conn's syndrome**.
- Differentiating between the two is important as this determines treatment.
- Adrenal carcinoma is an extremely rare cause of primary hyperaldosteronism

## **Features:**

- hypertension
- hypokalaemia (e.g. muscle weakness)
- alkalosis

## **Investigations:**

- 1) high serum aldosterone
- 2) low serum renin
- 3) high-resolution CT abdomen
- 4) adrenal vein sampling

## **Management:**

- 1) bilateral adrenocortical **hyperplasia**: aldosterone antagonist e.g. **spironolactone**
- 2) adrenal **adenoma** (**Conn's syndrome**): **surgery**

# Renin-angiotensin-aldosterone system (RAAS)

## Renin

- Renin is enzyme secreted by juxtaglomerular cells
- hydrolyses angiotensinogen to produce angiotensin I

### Factors stimulating renin secretion:

- 1) Hypotension causing reduced renal perfusion
- 2) Hyponatraemia
- 3) Sympathetic nerve stimulation
- 4) Catecholamines
- 5) Erect posture

### Factors reducing renin secretion:

- ☒ Drugs: beta-blockers, NSAIDs

## Angiotensin II

- Angiotensin-converting enzyme (ACE) in the **lungs** converts angiotensin I → angiotensin II
- Angiotensin II has a wide variety of actions:
  - 1) VC of vascular smooth muscle leading to raised blood pressure
  - 2) VC of efferent arteriole of the glomerulus → increased filtration fraction (FF) to preserve GFR. Remember that  $FF = GFR / \text{renal plasma flow}$
  - 3) Stimulates thirst (via the hypothalamus)
  - 4) Stimulates aldosterone and ADH release
  - 5) Increases proximal tubule  $Na^+/H^+$  activity

## Aldosterone

- released by the zona glomerulosa in response to raised angiotensin II, potassium, and ACTH levels
- causes retention of  $Na^+$  in exchange for  $K^+/H^+$  in distal tubule

# Cushing's syndrome

(Increased cortisol of any cause)

## Causes:

### A) ACTH dependent causes:

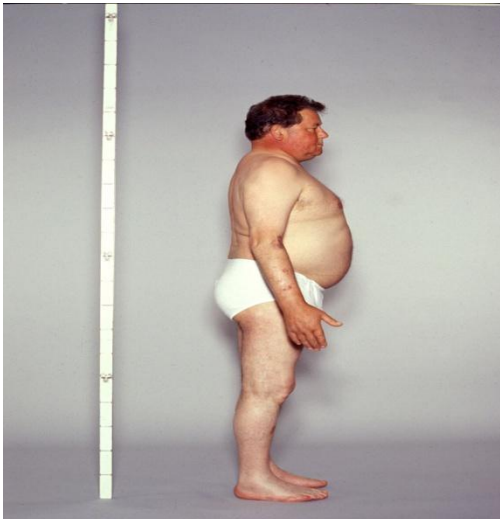
- 1) **Cushing's disease** (80%): **pituitary tumour secreting ACTH** ⇒ producing adrenal hyperplasia
- 2) **Ectopic ACTH production** (5-10%):  
e.g. **small cell lung cancer** (accounts 50-75% of case of ectopic ACTH)

### B) ACTH independent causes:

- 1) Iatrogenic: steroids
- 2) Adrenal adenoma (5-10%)
- 3) Adrenal carcinoma (rare)
- 4) Micronodular adrenal dysplasia (very rare)
- 5) Carney complex: syndrome including cardiac myxoma

## Features:

- 1) Central adiposity, plethoric complexion, abdominal striae
- 2) Thin arms and legs and bruising on the arms.
- 3) Hypertension, impaired glucose homeostasis or diabetes
- 4) Proximal muscle weakness (difficulty standing)
- 5) Menstrual irregularities



Thin skin and loss of subcutaneous fat is a sign of Cushing's disease

## Investigations

- Investigations are divided into confirming Cushing's syndrome and then localizing the lesion.
- A hypokalaemic metabolic alkalosis may be seen, along with impaired glucose tolerance.
- Ectopic ACTH secretion (e.g. SCLC) is characteristically associated with very low potassium levels.
- **An insulin stress test** is used to **differentiate between true Cushing's and pseudo-Cushing's**

### Tests to confirm Cushing's syndrome:

The two most commonly used tests are:

- 1) **Overnight dexamethasone suppression test (the most sensitive)** failing to suppress to less than 50 nmol/L confirms the diagnosis
- 2) **24 hr urinary free Cortisol:** good initial screening test

### Localisation tests:

- 1) **9 am and midnight plasma ACTH and cortisol levels: The first-line localisation.**  
If ACTH is suppressed then a non-ACTH dependent cause is likely as adrenal adenoma
- 2) **High-dose dexamethasone suppression test:**
  - if pituitary source then cortisol suppressed
  - if ectopic/adrenal then no change in Cortisol
- 3) **CRH stimulation:**
  - if pituitary source then cortisol rises
  - if ectopic/adrenal then no change in cortisol
- 4) **Petrosal sinus sampling of ACTH:**  
Differentiate between pituitary and ectopic ACTH secretion

### Pseudo-Cushing's: mimics Cushing's

- often due to **alcohol excess** or **severe depression**
- causes false positive dexamethasone suppression test or 24 hr urinary free cortisol
- insulin stress test may be used to differentiate

### Nelson's syndrome

- Occurs in approximately 30% of patients adrenalectomised for Cushing's disease.
- It is probably due to the clinical progression of the pre-existing pituitary adenoma after the restraint of hypercortisolism on adrenocorticotrophic hormone (ACTH) secretion is removed.
- Plasma ACTH levels are markedly elevated.
- Pituitary magnetic resonance imaging (MRI) defines the extent of the tumour.

## **Adrenal medulla**

- The adrenal medulla secretes virtually all the adrenaline in the body as well as secreting small amounts of noradrenaline.
- It essentially represents an enlarged and specialised sympathetic ganglion

## **Phaeochromocytoma**

- Phaeochromocytoma is a rare catecholamine secreting tumour.
- About 10% are familial and may be associated with:
  - ☒ MEN type II,
  - ☒ neurofibromatosis and
  - ☒ Von Hippel-Lindau syndrome.

### **Basics:**

- bilateral in 10%
  - malignant in 10%
  - extra-adrenal in 10%
- (The most common site is **organ of Zuckerkandl**, adjacent to the bifurcation of the aorta)

### **Features are typically episodic:**

- 1) hypertension (around 90% of cases, may be sustained)
- 2) headaches
- 3) palpitations
- 4) sweating
- 5) anxiety

### **Tests:**

- **24 hr urinary collection of metanephrines** (sensitivity 97%)
- This has replaced a 24 hr urinary collection of catecholamines (sensitivity 86%)

### **Management:**

- 1) **Surgery is the definitive management.**
- 2) The patient must first however be stabilized with medical management:
  - **alpha-blocker** (e.g. phenoxybenzamine), given before a beta-blocker (e.g. propranolol)

مهم جدا



## **Autoimmune polyendocrinopathy syndrome (APS)**

- Addison's disease (autoimmune hypoadrenalism) is associated with other endocrine deficiencies in approximately 10% of patients.
- There are two distinct types of autoimmune polyendocrinopathy syndrome (APS).

### **APS type 1 (MEDAC)** **(Very rare)**

- Occasionally referred to as **Multiple Endocrine Deficiency Autoimmune Candidiasis (MEDAC)**.
- It is a very rare **autosomal recessive disorder** caused by mutation of AIRE1 gene on chromosome 21

#### **Features of APS type 1:**

(2 out of 3 needed)

- 1) **chronic mucocutaneous candidiasis** (typically first feature as young child)
- 2) **Addison's disease**
- 3) **primary hypoparathyroidism**

☒ Primary hypoparathyroidism is usually the **first endocrine manifestation** of type 1 autoimmune polyendocrinopathy syndrome.

☒ The contrast to multiple endocrine neoplasia (MEN), where hyperparathyroidism is a common finding, should be noted

### **APS type 2 (Schmidt's syndrome)**

- sometimes referred to as **Schmidt's syndrome**
- **much more common**
- Has a **polygenic inheritance** and is linked to **HLA DR3/DR4**.
- Patients have **Addison's disease** plus either:
  - ☒ **type 1 DM** OR
  - ☒ **autoimmune thyroid disease**

✚ Vitiligo can occur in both types.

# Multiple endocrine neoplasia (MEN)

MEN is inherited as an **autosomal dominant**

The table below summarises the three main types of multiple endocrine neoplasia

| MEN type I                                                                                                                                                                                                                                                                                                                                                                | MEN type IIa                                                                                                               | MEN type IIb                                                                                                                                                |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>3 P's</b><br>1) <b>Parathyroid</b> (95%):<br><b>Hyperparathyroidism</b> due to parathyroid hyperplasia<br><br>2) <b>Pituitary</b> (70%)<br>e.g. Acromegaly, prolactinoma<br><br>3) <b>Pancreas</b> (50%): e.g. <ul style="list-style-type: none"> <li>insulinoma,</li> <li>gastrinoma (leading to recurrent peptic ulceration)</li> </ul><br>Also: adrenal and thyroid | 1) <b>Medullary thyroid cancer</b> (70%)<br><br><b>2 P's</b><br>2) <b>Phaeochromocytoma</b><br>3) <b>Parathyroid</b> (60%) | 1) <b>Medullary thyroid cancer</b><br><br><b>1 P</b><br>2) <b>Phaeochromocytoma</b><br>3) <b>Marfanoid body habitus</b><br><b>Neuromas</b> (tounge nodules) |
| MEN1 gene                                                                                                                                                                                                                                                                                                                                                                 | RET oncogene                                                                                                               | RET oncogene                                                                                                                                                |
| Most common presentation = <b>hypercalcaemia</b>                                                                                                                                                                                                                                                                                                                          |                                                                                                                            |                                                                                                                                                             |

## Medullary thyroid cancer

- Inherited forms of MTC are associated with germ-line mutations in the RET proto-oncogene and helpful in screening for familial disease in patients presenting with a new diagnosis of MTC.
- Calcitonin is a marker for MTC; persistent or rising levels suggest active disease.
- MTC is a life threatening disease that can be cured or prevented by early thyroidectomy.
- Medullary thyroid tumours do not concentrate radioiodine and must be treated with thyroidectomy.
- Patients with metastatic or recurrent disease are treated with chemotherapy or radiotherapy.



A 27-year-old male is referred to the clinic for further management of his poorly controlled blood pressure. He was diagnosed with hypertension two years previously and is currently on ramipril 10 mg daily, amlodipine 10 mg daily and bendroflumethiazide 2.5 mg per day.

On further questioning he stated that he has severe headache nearly every morning and excessive sweating. His partner said that he has become increasingly nervous and agitated for the last six months.

On examination, his pulse rate is 100 beats per minute and his blood pressure is 170/100. Cardiovascular, respiratory and abdominal examination were normal.

Investigations show:

|                                 |                             |
|---------------------------------|-----------------------------|
| <b>Sodium</b>                   | <b>140 mmol/l</b>           |
| <b>Potassium</b>                | <b>3.5 mmol/l</b>           |
| <b>Creatinine</b>               | <b>120 mol/l</b>            |
| <b>Calcium</b>                  | <b>2.91 mmol/l</b>          |
| <b>Phosphate</b>                | <b>0.6 mmol/l</b>           |
| <b>Urine free metadrenaline</b> | <b>15 mol/24 hr (&lt;5)</b> |

MRI scan of the abdomen revealed a 4 cm mass in the left adrenal gland.

Bearing the possible diagnosis in mind, what is the most appropriate additional investigation to confirm the diagnosis?

|                                  |                                      |
|----------------------------------|--------------------------------------|
| <input type="radio"/>            | PTH concentration                    |
| <input checked="" type="radio"/> | Pentagastrin stimulation test        |
| <input type="radio"/>            | Fasting plasma calcitonin            |
| <input type="radio"/>            | Ultrasound scan of the thyroid gland |
| <input type="radio"/>            | Genetic screening                    |

This patient presented with poorly controlled blood pressure despite three medications, headache, sweating, nervousness and agitation which all point towards pheochromocytoma. His investigations show high urine free metadrenaline (which confirms the diagnosis of pheochromocytoma) and hypercalcaemia with hypophosphataemia which points towards hyperparathyroidism. So, to confirm the diagnosis of multiple endocrine neoplasia (MEN) type 2a, screening for medullary thyroid carcinoma should be done by **pentagastrin stimulation test** which demonstrates a rise in calcitonin concentration (secreted by C cells of the thyroid) following pentagastrin administration.

# **Hypokalaemia and hypertension**

For exams it is useful to be able to classify the causes of hypokalaemia in to those associated with hypertension, and those which are not

## **Hypokalaemia with hypertension:**

- Cushing's syndrome
- Conn's syndrome (primary hyperaldosteronism)
- Liddle's syndrome (similar to hyperaldosteronism)
- 11-beta hydroxylase deficiency\*

\*21-hydroxylase deficiency, which accounts for 90% of congenital adrenal hyperplasia cases, is not associated with hypertension

**Carbenoxolone** (an anti-ulcer drug) and **liquorice excess** can potentially cause hypokalaemia associated with hypertension

## **Hypokalaemia without hypertension:**

- GI loss (e.g. Diarrhoea, vomiting)
- Diuretics
- Renal tubular acidosis (type 1 and 2)
- Bartter's syndrome
- Gitelman syndrome

**\*\*type 4 renal tubular acidosis is associated with hyperkalaemia**

## **Bartter's syndrome**

- Autosomal recessive
- Causes **severe hypokalaemia**
- It is due to defective chloride absorption at the  $\text{Na}^+ \text{K}^+ 2\text{Cl}^-$  cotransporter (NKCC2) in the ascending loop of Henle (like furosemide).
- It should be noted that it is associated with **normotension** (unlike other endocrine causes of hypokalaemia such as Conn's, Cushing's and Liddle's syndrome which are associated with hypertension).

Loop diuretics work by inhibiting NKCC2  
think of Bartter's syndrome as like taking large doses of furosemide

### **Features:**

- Usually presents in childhood, e.g. Failure to thrive
- Polyuria, polydipsia
- Hypokalaemia
- Normotension
- Weakness

## **Gitelman's syndrome**

Gitelman's syndrome is due to a defect in the **thiazide-sensitive  $\text{Na}^+ \text{Cl}^-$  transporter** in the distal convoluted tubule.

### **Features:**

- 1) hypokalaemia ( $\downarrow\downarrow \text{K}$ )
- 2) hypomagnesaemia ( $\downarrow\downarrow \text{Mg}$ )
- 3) hypocalciuria (low Ca in urine)
- 4) metabolic alkalosis
- 5) **normotension**

## **Liddle's syndrome**

- a rare **autosomal dominant** condition
- Causes **hypertension** and hypokalaemic alkalosis.
- It is thought to be caused by **disordered sodium channels** in the distal tubules leading to increased reabsorption of sodium. (similar to hyperaldosteronism)
- Treatment is with either **amiloride** or **triamterene**.

## Thyroid Gland

### Thyroid function tests:

| Diagnosis                                                             | TSH            | Free T4        | Notes                                                                            |
|-----------------------------------------------------------------------|----------------|----------------|----------------------------------------------------------------------------------|
| Thyrotoxicosis<br>(e.g. Graves' disease)                              | Low            | High           | In T3 thyrotoxicosis the free T4 will be normal                                  |
| Over-replacement with thyroxine                                       | Low            | High           | fT3 Normal or high                                                               |
| TSH-secreting tumour                                                  | High           | High           | fT3 High                                                                         |
| Untreated hypopituitarism<br>(Secondary hypothyroidism)               | Low/Low normal | Low/Low normal | fT3 Low/Low normal<br>Replacement steroid therapy is required prior to thyroxine |
| Primary hypothyroidism<br>(primary atrophic hypothyroidism)           | High           | Low            |                                                                                  |
| Sick euthyroid syndrome<br>(now referred to as non-thyroidal illness) | Low**          | Low            | Common in hospital inpatients<br>T3 is particularly low in these patients        |
| Subclinical hypothyroidism                                            | High           | Normal         |                                                                                  |
| Poor compliance with thyroxine                                        | High           | Normal         |                                                                                  |
| Steroid therapy                                                       | Low            | Normal         | Similar to (Subclinical hyperthyroid)                                            |

\*\*TSH may be normal in some cases

### Non compliant

The TSH level is high. This implies that over recent days/weeks her body is thyroxine deficient. However, her free T4 is within normal range. The most likely explanation is that she started taking the thyroxine properly just before the blood test. This would correct the thyroxine level but the TSH takes longer to normalize.

If free T4 and T3 are high, but TSH is normal or high, a pituitary MRI should be done to look for a pituitary mass (**TSH-secreting adenoma**)

# **Thyrotoxicosis**

## **Causes:**

- 1) Graves' disease (toxic diffuse goitre) accounts for 50-60% of cases of thyrotoxicosis.
- 2) toxic nodular goitre
- 3) toxic adenoma (Plummer's disease)
- 4) subacute (de Quervain's) thyroiditis
- 5) post-partum thyroiditis
- 6) acute phase of Hashimoto's thyroiditis (later results in hypothyroidism)
- 7) amiodarone therapy

## **Investigation:**

- 1) TSH down, T4 and T3 up
- 2) thyroid autoantibodies
- 3) other investigations are not routinely done but includes isotope scanning

## **Radioactive uptake thyroid scan:**

- Graves' disease is associated with diffusely increased radioactive uptake in the thyroid.
- A solitary hot nodule demonstrates increased uptake in one area, with decreased uptake elsewhere,
- Toxic multinodular goitre, multiple areas of increased uptake.
- In thyrotoxicosis factitia, uptake is globally reduced.

Frequently lowish white blood cells (WBC) are noted in thyrotoxicosis per se, as well as following the introduction of thionamides, and this is not an indication to stop therapy. However, therapy should be stopped if there is a demonstrable **neutropenia/agranulocytosis with neutrophil count below  $1.5 \times 10^9/L$  (1.5-7).**

**Carbimazole-induced agranulocytosis** (neutrophil count below  $0.5 \times 10^9/L$ ) is fortunately rare, but life threatening. Thionamides should be withdrawn, infection treated with appropriate antibiotics (broad spectrum cephalosporin) and occasionally, granulocyte colony-stimulating factor (G-CSF) is required when white count fails to respond.

# Graves' disease

- Graves' disease is the most common cause of thyrotoxicosis.
- It is typically seen in women aged 30-50 years.

## Features:

- typical features of thyrotoxicosis
- specific signs limited to Grave's:
  - 1) **eye signs** (30% of patients): exophthalmos, ophthalmoplegia
  - 2) **pretibial myxoedema**
  - 3) **thyroid acropachy**:
    - subperiosteal new bone formation, (aka Marie's Disease).
    - Most commonly manifests as clubbing of the fingers and toes with soft tissue swelling.
    - It is sometimes associated with Graves' disease but not with other causes of hyperthyroidism
    - No effective treatment for acropachy.

## Autoantibodies:

- 1) **Anti-TSH receptor stimulating antibodies** (90%)
- 2) **Anti-thyroid peroxidase antibodies** (50%)

## Graves' disease management:

- Despite many trials there is no clear guidance on the optimal management of Graves' disease
- **Treatment options include:**
  - 1) titration of anti-thyroid drugs (ATDs, for example carbimazole),
  - 2) block-and-replace regimes,
  - 3) Radioiodine treatment and
  - 4) Surgery.
  - 5) Propranolol is often given initially to block adrenergic effects

## Anti-thyroid drugs (ATD) titration:

- **carbimazole** is started at 40mg and reduced gradually to maintain euthyroidism
- typically continued for 12-18 months
- patients following an ATD titration regime have been shown to suffer fewer side-effects than those on a block-and-replace regime
- The major complication of carbimazole therapy is **agranulocytosis**.

## Block-and-replace:

- **carbimazole** is started at 40mg
- thyroxine is added when the patient is euthyroid
- treatment typically lasts for 6-9 months

## Radioiodine treatment: Goiter shrinkage may occur in up to 30% following RAI.

### ⊗ **Contraindications** include:

- 1) Pregnancy (should be avoided for 4-6 months following treatment) and
- 2) Age < 16 years.
- 3) Thyroid eye disease is a relative contraindication, as it may worsen the condition

- ⊗ the proportion of patients who become hypothyroid depends on the dose given, but as a rule the **80%** majority of patient will require thyroxine supplementation after 5 years

## **Thyroid eye disease**

Thyroid eye disease affects between 25-50% of patients with Graves' disease.

### **Pathophysiology:**

- it is thought to be caused by an autoimmune response against an autoantigen, possibly the TSH receptor → retro-orbital inflammation → results in **glycosaminoglycan** and **collagen deposition** in the muscles

### **Prevention:**

- **smoking** is the most important modifiable risk factor for development of thyroid eye disease

### **Features:**

- 1) the patient may be eu-, hypo- or hyperthyroid at the time of presentation
- 2) exophthalmos
- 3) ophthalmoplegia
- 4) conjunctival oedema (chemosis)
- 5) optic disc swelling
- 6) Inability to close the eye lids may lead to sore, dry eyes. If severe and untreated patients can be at risk of exposure keratopathy

### **Management:**

- 1) Topical lubricants may be needed to help prevent corneal inflammation caused by exposure
- 2) Steroids
- 3) Radiotherapy
- 4) Surgery

### **Treatment for malignant exophthalmos:**

- 1) rapid administration of steroids
- 2) Where sight is threatened, orbital decompression may be necessary

### **Monitoring patients with established thyroid eye disease:**

The following symptoms/signs should indicate the need for urgent review by an ophthalmologist (see EUGOGO guidelines):

- 1) unexplained deterioration in vision
- 2) awareness of change in intensity or quality of colour vision in one or both eyes
- 3) history of eye suddenly 'popping out' (globe subluxation)
- 4) obvious corneal opacity
- 5) cornea still visible when the eyelids are closed
- 6) disc swelling

### **Radioiodine treatment:**

- May increase the inflammatory symptoms seen in thyroid eye disease.
- In a recent study of patients with Graves' disease around 15% developed, or had worsening of, eye disease.(can lead to malignant exophthalmos )
- Prednisolone may help reduce the risk (Patients with thyroid eye disease are generally treated with steroids for 1 to 2 weeks prior to starting radioiodine therapy.



**This is pre-tibial myxoedema with slightly raised, pinkish, indurated patches usually on the fronts of the shins or dorsum of the foot and often associated with acropachy.**



## Toxic Multinodular Goiter

- A thyroid gland that contains a **number of autonomously functioning thyroid nodules** that **secrete excess thyroid hormones**.
- Nuclear scintigraphy reveals patchy uptake. (multiple areas of increased uptake)
- A solitary hot nodule demonstrates increased uptake in one area, with decreased uptake elsewhere.
- The treatment of choice is **radioiodine therapy**.

## Subacute (De Quervain's) thyroiditis

- Thought to occur following viral infection and
- typically presents with hyperthyroidism

### Features:

- 1) Hyperthyroidism:
  - ☒ Marked constitutional symptoms - **weight loss** in particular and
  - ☒ thyroid function tests are often normal
- 2) Painful goiter:
  - ☒ thyroid enlargement is typically rapid, occurring over a period of days
- 3) raised **ESR**
- 4) **globally reduced uptake** on iodine-131 scan

Thyrotoxicosis is related to increased release of stored thyroid hormone rather than increased production of thyroid hormone. As such carbimazole and propylthiouracil are ineffective.

### Management:

- ☒ usually self-limiting - most patients do not require treatment
- ☒ thyroid pain may respond to **aspirin** or other **NSAIDs**
- ☒ **Propranolol** is the most appropriate treatment for transient symptoms of hyperthyroidism.
- ☒ in more severe cases **steroids** are used to reduce inflammation, particularly if hypothyroidism develops
- ☒ Hypothyroidism is usually mild but persists for 2-4 months.
- ☒ A few patients (~5%) remain hypothyroid and need long term thyroid hormone replacement.
- ☒ Recurrences are uncommon.

ملحوظة مهمة انك بتدى كورتزون مش ثيروكسين

# Thyroid Storm

- Thyroid storm is a rare but life-threatening complication of thyrotoxicosis.
- It is typically seen in patients with established thyrotoxicosis and is rarely seen as the presenting feature.
- Iatrogenic thyroxine excess **does not** usually result in thyroid storm

## Features:

- 1) fever > 38.5 C
- 2) tachycardia
- 3) hypertension
- 4) heart failure
- 5) confusion and agitation
- 6) nausea and vomiting
- 7) abnormal LFTs

## Management:

- 1) symptomatic treatment e.g. paracetamol
- 2) treatment of underlying precipitating event
- 3) **propranolol**
- 4) **anti-thyroid drugs**: e.g. **methimazole** or **propylthiouracil**
- 5) **Lugol's iodine**
- 6) **dexamethasone** - e.g. 4mg IV qds (4x4) - blocks the conversion of T4 to T3

# Subclinical Hyperthyroidism

- Subclinical hyperthyroidism is an entity which is gaining increasing recognition.
- **It is defined as:**
  - normal serum free thyroxine and triiodothyronine levels
  - with a thyroid stimulating hormone (TSH) below normal range (usually < 0.1 mu/l)

Normal T3, T4  
Low TSH

## Causes:

- ✓ multinodular goiter, particularly in elderly females
- ✓ excessive thyroxine may give a similar biochemical picture
- The importance in recognising subclinical hyperthyroidism lies in the potential effect on the **cardiovascular system** (**atrial fibrillation**) and **bone metabolism** (**osteoporosis**).
- It may also impact on quality of life and **increase the likelihood of dementia**

## Management:

- TSH levels often revert to normal - therefore levels must be persistently low to warrant intervention
- a reasonable treatment option is **a therapeutic trial of low-dose antithyroid** agents for approximately 6 months in an effort to induce a remission

# Hypothyroidism

- Hypothyroidism affects around 1-2% of women in the UK
- 5-10 times more common in females than males.

## A) Primary hypothyroidism:

### 1) Primary atrophic hypothyroidism:

- most common cause
- autoimmune disease,
- associated with type I DM, Addison's or pernicious anaemia
- 5 times more common in women

### 2) Hashimoto's thyroiditis:

- autoimmune disease as above with **goiter** (positive **microsomal antibodies**)
- may cause **transient thyrotoxicosis** in the acute phase
- 10 times more common in women

### 3) After **thyroidectomy** or **radioiodine** treatment

### 4) Drug therapy (e.g. **lithium**, **amiodarone** or **anti-thyroid drugs** such as carbimazole)

### 5) Dietary **iodine deficiency**

## B) Secondary hypothyroidism (rare):

- From pituitary failure.
- Other associated conditions:
  - 1) Down's syndrome
  - 2) Turner's syndrome
  - 3) coeliac disease

# Hashimoto's thyroiditis

- Autoimmune disorder of the thyroid gland.
- chronic lymphocytic thyroiditis
- It is typically associated with hypothyroidism although there may be a transient thyrotoxicosis in the acute phase.
- It is 10 times more common in women

## Features:

- features of hypothyroidism
- goiter: firm, non-tender
- anti-thyroid peroxidase and also anti-Tg antibodies, anti-microsomal antibodies

Hashimoto's thyroiditis = hypothyroidism + goiter + anti-TPO

### Hypothyroidism management:

- Initial starting dose of levothyroxine should be lower in elderly patients and those with ischaemic heart disease.
- The BNF recommends that for patients with **cardiac disease**, **severe hypothyroidism** or **patients over 50 years** the initial starting dose should be **25mcg od** with dose slowly titrated.
- **Other patients** should be started on a dose of **50-100 mcg od**
- following a change in thyroxine dose thyroid function tests should be checked after 8-12 weeks
- The therapeutic goal is 'normalisation' of the thyroid stimulating hormone (TSH) level.
- A TSH value **0.5-2.5 mU/l** is the preferable range
- There is **no evidence to support combination therapy with levothyroxine and liothyronine**

### Side-effects of thyroxine therapy:

- 1) hyperthyroidism: due to over treatment
- 2) reduced bone mineral density
- 3) CVS: worsening of angina, atrial fibrillation

### Interactions:

- iron: absorption of levothyroxine reduced, give at least 2 hours apart

### Subclinical hypothyroidism

- TSH raised but T3, T4 normal
- no obvious symptoms

### Significance:

- risk of progressing to overt hypothyroidism is 2-5% per year (higher in men)
- risk increased by presence of thyroid autoantibodies
- Treat if:
  - 1) **TSH > 10**
  - 2) **thyroid autoantibodies positive**
  - 3) **other autoimmune disorder**
  - 4) **previous treatment of Graves' disease**

### Sick euthyroid syndrome:

- In sick euthyroid syndrome (now referred to as non-thyroidal illness) it is often said that everything (TSH, thyroxine and T3) is low.
- In the majority of cases however the TSH level is within the normal range (inappropriately normal given the low thyroxine and T3).
- Changes are reversible upon recovery from the systemic illness.

### Pendred's syndrome:

- Autosomal recessive disorder of defective iodine uptake
- sensorineural deafness
- goiter
- euthyroid or mild hypothyroidism

## **Skin disorders associated with thyroid disease**

### **A) Skin manifestations of hypothyroidism:**

- 1) dry, coarse scalp hair, loss of lateral aspect of eyebrows
- 2) dry (anhydrosis), cold, yellowish skin
- 3) non-pitting oedema (e.g. hands, face)
- 4) eczema
- 5) xanthomata

### **B) Skin manifestations of hyperthyroidism:**

- 1) pretibial myxoedema: erythematous, oedematous lesions above the lateral malleoli
- 2) thyroid acropachy: clubbing
- 3) scalp hair thinning
- 4) increased sweating

### **C) Pruritus can occur in both hyper- and hypothyroidism**

## **Goiter & Nodules**

- Thyroidal neck swellings can be due to goitre or nodules and can be present in hypothyroid, euthyroid or hyperthyroid states.
- **Goiters occur either;**
  - ☒ when there is a high level of thyroid-stimulating hormone (TSH) stimulating thyroidal growth or
  - ☒ when there is a problem with the production of thyroid hormones, such as occur during iodine deficiency
- Goiters can involve all or part of the gland.

### **The differential diagnosis of a goiter includes**

- 1) iodine deficiency,
  - 2) Graves' disease,
  - 3) toxic multinodular goiter, and
  - 4) Hashimoto's thyroiditis.
- If excessively large, a goiter may cause respiratory difficulties which need urgent attention.
  - Patients with suspected retrosternal extension of a goiter should be considered for urgent imaging and a **flow-volume loop**.
  - Occasionally, a single nodule, or toxic adenoma, can be present which on isotope scanning can be 'hot' (producing T3 and T4) or 'cold'.
  - Hot nodules are rarely malignant but can cause thyrotoxicosis.
  - They generally respond well to surgery or radioiodine treatment.
  - A cold nodule is more concerning as around 20% of cases are malignant. Patients need urgent referral for biopsy.

# Thyroid Cancer

Features of hyperthyroidism or hypothyroidism are **not commonly** seen in patients with thyroid malignancies as they rarely secrete thyroid hormones

PFMAL

| Type              | Percentage  |                                                                                                                                         |
|-------------------|-------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| <b>Papillary</b>  | <b>70%</b>  | <ul style="list-style-type: none"><li>• Often young females</li><li>• excellent prognosis</li></ul>                                     |
| <b>Follicular</b> | <b>20%</b>  |                                                                                                                                         |
| <b>Medullary</b>  | <b>5%</b>   | <ul style="list-style-type: none"><li>• Cancer of parafollicular cells,</li><li>• secrete calcitonin,</li><li>• part of MEN-2</li></ul> |
| <b>Anaplastic</b> | <b>1%</b>   | <ul style="list-style-type: none"><li>• Not responsive to treatment( palliative TTT),</li><li>• can cause pressure symptoms</li></ul>   |
| <b>Lymphoma</b>   | <b>Rare</b> | Associated with Hashimoto's                                                                                                             |

## Papillary and follicular cancer

### Management:

- 1) **total thyroidectomy**
- 2) Followed by **radioiodine** (I-131) to kill the normal thyroid tissue remnants and microscopic foci of residual tumour.
- 3) yearly **thyroglobulin** levels to detect early recurrent disease

## Medullary thyroid tumours

- Do not concentrate radioiodine and must be treated with **thyroidectomy**.
- Metastatic or recurrent disease is treated with **chemotherapy or radiotherapy**.
- Because it is caused by C cell proliferation which are not TSH-responsive, levothyroxine is not effective in treatment

Anaplastic thyroid cancer - aggressive, difficult to treat and often causes pressure symptoms

## **Follicular thyroid carcinoma (FTC)**

- A well-differentiated tumour. FTC resembles the normal microscopic pattern of the thyroid.
- FTC originates in follicular cells and is the second most common cancer of the thyroid after papillary carcinoma.
- The most common presentation of thyroid cancer is an asymptomatic thyroid mass, or nodule
- The staging of well-differentiated thyroid cancers is related to age for the first and second stages but not related for the third and fourth stages.

### **Younger than 45 years:**

- 1) Stage I - Any T, any N, M0 (Cancer is in the thyroid only).
- 2) Stage II - Any T, any N, M1 (Cancer has spread to distant organs).

### **Older than 45 years:**

- 1) Stage I - T1, N0, M0 (Cancer is in the thyroid only and may be found in one or both lobes).
  - 2) Stage II - T2, N0, M0 and T3, N0, M0 (Cancer is in the thyroid only and is larger than 1.5 cm).
  - 3) Stage III - T4, N0, M0 and any T, N1, M0 (Cancer has spread outside the thyroid but not outside of the neck).
  - 4) Stage IV - Any T, any N, M1 (Cancer has spread to other parts of the body).
- Surgery is the definitive management of thyroid cancer.
  - Various types of operations may be performed.
  - Lobectomy with isthmectomy is the minimal operation for a potentially malignant thyroid nodule
  - Patients less than 40 years who have FTC nodules less than 1 cm, well defined, minimally invasive, and isolated may be treated with hemithyroidectomy and isthmectomy.
  - If feasible, subtotal thyroidectomy (small part of contralateral lobe retained) is preferable since it carries a lower incidence of complications (for example, hypoparathyroidism, superior and/or recurrent laryngeal nerve injury).
  - Approximately 10% of patients who have had total thyroidectomy (removal of all thyroid tissue preserving the contralateral parathyroid glands) demonstrate cancer in the contralateral lobe.
  - **Total thyroidectomy:**
    - ⇒ Should be performed in patients who are more than 40 years with FTC and in any patient with bilateral disease.
    - ⇒ Recommended for any patient with a thyroid nodule and a history of irradiation.
  - Some studies show lower recurrence rates and increased survival rates in patients who have undergone total thyroidectomy.

- This surgical procedure also facilitates earlier detection and treatment of recurrent or metastatic carcinoma.
- Patients receive **radioiodine** four to six weeks after thyroidectomy to detect and destroy any metastases and any residual tissue in the thyroid.
- Following thyroidectomy, patients will need to take **thyroid replacement therapy**.

#### **External beam radiation:**

- ⇒ Used in the management of FTC if the cancer cannot be resected, or if there is extension into adjacent structures.
- ⇒ may be administered postoperatively to reduce the risk of local-regional recurrence
- ⇒ It may also be used palliatively to treat pain from bone metastases.
- **Chemotherapy** with cisplatin or doxorubicin has limited efficacy. It may be employed when other treatment modalities have failed.



## **Pregnancy Thyroid Problems**

- In pregnancy there is an **increase** in the levels of **thyroxine-binding globulin** (TBG).
- This causes an increase in levels of total thyroxine but does not affect the free thyroxine level

### **Thyrotoxicosis In pregnancy**

- Untreated thyrotoxicosis increases the risk of maternal heart failure, fetal loss and premature labour.
- Graves' disease is the most common cause of thyrotoxicosis in pregnancy.
- **transient gestational hyperthyroidism** may also occur:
  - ⇒ Activation of TSH receptor by HCG (with suppression of TSH).
  - ⇒ HCG levels will fall in second and third trimester

#### **Management:**

- **Propylthiouracil** has traditionally been **the antithyroid drug of choice**.
- It is suggested to switch from PTU to an equivalent dose of **carbimazole** after 1<sup>st</sup> trimester.
- Thyroid function testing should be performed 2 to 4 weeks after switching to carbimazole to be sure that a euthyroid state has been maintained then every 4 weeks.
- **Teratogenic effects** of carbimazole are not well proven, but they are potentially serious and are **confined to 1st trimester**.
- After 1st trimester, potential risk of PTU associated **hepatotoxicity**, although extremely rare, is thought to outweigh any potential risks of carbimazole.
- **maternal free thyroxine** levels should be kept in **the upper third of the normal** reference range **to avoid fetal hypothyroidism**
- **thyrotrophin receptor stimulating antibodies** should be checked at **30-36 wks gestation**
  - ⇒ helps to determine risk of neonatal thyroid problems
- block-and-replace regimes **should not be used in pregnancy**
- radioiodine therapy is **contraindicated**

### **Hypothyroidism In pregnancy**

- 1) thyroxine is safe during pregnancy & breast feeding
- 2) serum TSH measured in each trimester and 6-8 weeks post-partum
- 3) some women require an increased dose of thyroxine during pregnancy

### **Post-partum thyroiditis (5%)**

- **Transient hyperthyroidism** usually 2 to 6 months postpartum followed by **hypothyroidism** which also usually resolves but permanent hypothyroidism may occur.
- The exact aetiology is unknown but lymphocytic infiltration of the thyroid is typical, suggesting auto-immunity. TPO antibodies are found in 90% of patients

#### **3 stages:**

- 1) Thyrotoxicosis
- 2) Hypothyroidism
- 3) Normal thyroid function (but high recurrence rate in future pregnancies)

#### **Management**

- 1) The thyrotoxic phase is not usually treated with antithyroid drugs as the thyroid is not overactive.
- 2) **Propranolol** is typically used for symptom control
- 3) The hypothyroid phase is usually treated with **thyroxine**

# Thymoma

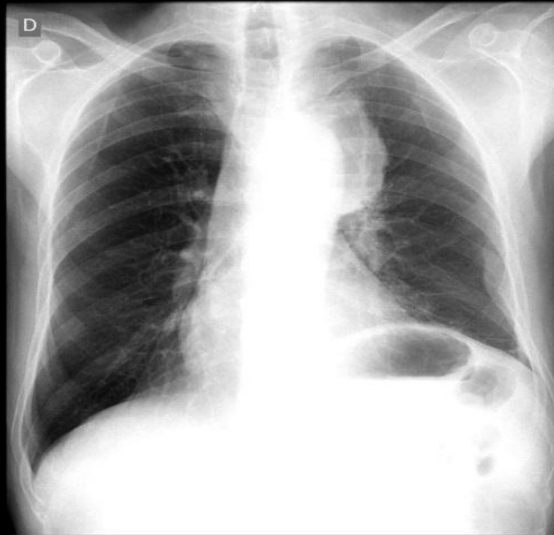
- Thymomas are the most common tumour of the anterior mediastinum
- Usually detected between the sixth and seventh decades of life.

## Associated with:

- 1) **myasthenia gravis** (30-40% of patients with thymoma)
- 2) **red cell aplasia**
- 3) dermatomyositis
- 4) also : SLE, SIADH

## Causes of death:

- 1) airway compression
- 2) **cardiac tamponade**



Chest x-ray and accompanying CT scan of a patient with a thymoma. In the chest x-ray there is a partially delineated mediastinal mass (anterior mediastinum) with regular borders, bulging the left upper mediastinal contour.



CT slice at the bifurcation of the main bronchus showing an invasive thymoma presenting as an anterior mediastinal mass



# **Diabetes Mellitus**

- Compared with subjects with normoglycaemia, beta cell mass is reduced by 50% in subjects with Impaired Fasting Glucose, by 65% in subjects with Type 2 diabetes, and over 90% in subjects with type 1 diabetes.

## **Type 1 DM**

- caused by **autoimmune destruction of the Beta-cells** of the pancreas
- Identical twins show **a genetic concordance of 40%**.
- **antibodies** against beta cells of pancreas
- It is inherited in a **polygenic fashion**
- **HLA DR4 > HLA DR3**
- **various antibodies** are detected in patients who later go on to develop type 1 DM such as:
  - 1) Islet-associated antigen (**IAA**) **antibody** and
  - 2) Glutamic acid decarboxylase (**GAD**) **antibody (in 70-90% of type 1 DM patients)**Their prognostic significance is not yet clear

## **Type 2 diabetes mellitus** (Islet amyloid deposition)

- **It is thought to be caused by:**
  - ✓ A relative deficiency of insulin and
  - ✓ The phenomenon of insulin resistance.
- Age, obesity and ethnicity are important aetiological factors.
- There is almost **100% concordance in identical twins**
- **NO HLA associations**
- Haemochromatosis is an example of secondary diabetes

## **Diabetes mellitus type 2 Diagnosis:**

- The diagnosis can only be made by either a plasma glucose or HbA1c sample.
- Diagnostic criteria vary according to whether the patient is symptomatic (polyuria, polydipsia etc) or not.

### **If the patient is symptomatic:**

- **fasting** glucose greater than or equal to **≥ 7.0** mmol/l (126)
- **random** glucose greater than or equal to **≥ 11.1** mmol/l (200) (or after 75g OGTT)

### **If the patient is asymptomatic:**

- ✓ The above criteria apply but must be demonstrated on **two separate occasions**.

In 2011 WHO released supplementary guidance on **the use of HbA1c on the diagnosis of DM:**

- 1) a HbA1c of greater than or equal to 6.5% (48 mmol/mol) is diagnostic of diabetes mellitus
- 2) a HbA1c value of less than 6.5% does not exclude diabetes (i.e. it is not as sensitive as fasting samples for detecting diabetes)
- 3) in patients without symptoms, the test must be repeated to confirm the diagnosis
- 4) it should be remembered that misleading HbA1c results can be caused by increased red cell turnover (see below)

### Conditions where HbA1c may not be used for diagnosis:

- 1) haemoglobinopathies
- 2) haemolytic anaemia
- 3) untreated iron deficiency anaemia
- 4) suspected gestational diabetes
- 5) children
- 6) HIV
- 7) CKD

### Impaired fasting glucose (IFG):

- ✓ A fasting glucose **6.1 - 6.9 mmol/l** (110-126)

### Impaired glucose tolerance:

- ✓ Fasting plasma glucose < 7.0 mmol/l (126) and
- ✓ OGTT 2-hour value **7.8 - 11 mmol/l** (140-200)
- Diabetes UK suggests people with IFG should then be offered an OGTT to rule out a diagnosis of diabetes.
- ✚ impaired fasting glucose (IFG) - due to hepatic insulin resistance
- ✚ impaired glucose tolerance (IGT) - due to muscle insulin resistance
- ✚ patients with **IGT** are more likely to develop T2DM and CVD than patients with IFG

### Acarbose:

In the STOP-NIDDM study shows;

- 1) a reduction in risk of new onset type 2 diabetes of 25%,
- 2) acarbose was associated with a 49% reduction in cardiovascular events.
- 3) Out of all the agents trialled in impaired glucose tolerance it is the only one so far to have demonstrated cardiovascular outcomes, albeit in a small number of patients.

### Glycosylated hemoglobin:

- Glycosylated haemoglobin (HbA1c) is the most widely used measure of long-term glycaemic control in DM.
- HbA1c is produced by the glycosylation of haemoglobin at a rate proportional to the glucose concentration.
- **The level of HbA1c therefore is dependent on:**
  - RBCs lifespan
  - average blood glucose concentration

### A number of conditions can interfere with accurate HbA1c interpretation:

| Lower-than-expected levels of HbA1c<br>(due to <b>reduced</b> red blood cell lifespan) | Higher-than-expected levels of HbA1c<br>(due to <b>increased</b> red blood cell lifespan) |
|----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Sickle-cell anaemia<br>GP6D deficiency<br>Hereditary spherocytosis                     | Vitamin B12/folic acid deficiency<br>Iron-deficiency anaemia<br>Splenectomy               |

- HbA1c is generally thought to reflect the blood glucose over the previous '**2-3 months**' although there is some evidence it is weighed more strongly to glucose levels of the past 2-4 weeks
- The relationship between HbA1c and average blood glucose is complex but has been studied by the Diabetes Control and Complications Trial (DCCT).
- A new internationally standardised method for reporting HbA1c has been developed by the International Federation of Clinical Chemistry (IFCC).
- This will report HbA1c in mmol per mol of haemoglobin without glucose attached.

| HbA1c (%) | Average plasma glucose (mmol/l) | IFCC-HbA1c (mmol/mol) |
|-----------|---------------------------------|-----------------------|
| 5         | 5.5                             |                       |
| 6         | 7.5                             | 42                    |
| 7         | 9.5                             | 53                    |
| 8         | 11.5                            | 64                    |
| 9         | 13.5                            | 75                    |
| 10        | 15.5                            |                       |
| 11        | 17.5                            |                       |
| 12        | 19.5                            |                       |

From the above we can see that **average plasma glucose = (2 \* HbA1c) - 4.5**

## **Prediabetes and impaired glucose regulation**

- Prediabetes is a term which is increasingly used where there is impaired glucose levels which are above the normal range but not high enough for a diagnosis of diabetes mellitus.
- The term includes patients who have been labeled as having either **impaired fasting glucose** (IFG) or **impaired glucose tolerance** (IGT).
- Diabetes UK estimate that around 1 in 7 adults in the UK have prediabetes.
- Many individuals with prediabetes will progress on to developing type 2 diabetes mellitus (T2DM) and they are therefore at greater risk of microvascular and macrovascular complications.

### **Terminology:**

- Diabetes UK currently recommends using the term prediabetes when talking to patients and impaired glucose regulation when talking to other healthcare professionals.
- research has shown that the term 'prediabetes' has the most impact and is most easily understood

### **Identification of patients with prediabetes:**

- NICE recommend using a validated computer based risk assessment tool for:
  - ⇒ all adults aged 40 and over,
  - ⇒ people of South Asian and Chinese descent aged 25-39, and
  - ⇒ adults with conditions that increase the risk of type 2 diabetes
- patients identified at high risk should have a blood sample taken
- a fasting plasma glucose of 5.5-6.9 mmol/l (100-125) or an HbA1c level of 42-47 mmol/mol (6.0-6.4%) indicates high risk

### **Management:**

- 1) lifestyle modification: weight loss, increased exercise, change in diet
- 2) at least **yearly** follow-up with blood tests is recommended
- 3) NICE recommend **metformin for adults at high risk** 'whose blood glucose measure (fasting plasma glucose or HbA1c) shows they are still progressing towards type 2 diabetes, despite their participation in an intensive lifestyle-change programme'

# **MODY**

- Maturity-onset diabetes of the young (MODY) is characterised by the development of type 2 diabetes mellitus in patients **< 25 years** old.
- It is typically inherited as an **autosomal dominant condition**.
- Over six different genetic mutations have so far been identified as leading to MODY.
- It is thought that around 1-2% of patients with diabetes mellitus have MODY, and around 90% are misclassified as having either type 1 or type 2 diabetes mellitus.

## **MODY 2:**

- 20% of cases
- due to a defect in the glucokinase gene

## **MODY 3:**

- 60% of cases
- due to a defect in the HNF-1 alpha gene (hepatocyte nuclear factor 1 homeobox A)

## **MODY-5:**

- Due to a mutation in HNF-1 $\beta$ .
- This mutation leads to the formation of **multiple cysts in both the kidneys and the liver**.
- It also leads to the development of abnormal glucose tolerance and eventually diabetes mellitus, which can occur at any age from toddler to young adults.

**(DD: APCKD)**

## **Features of MODY:**

- 1) typically develops in patients < 25 years
- 2) a family history of early onset diabetes is often present
- 3) ketosis is not a feature at presentation
- 4) patients with the most common form are **very sensitive to sulfonylureas**, insulin is not usually necessary

MODY 2 and MODY 3 are the most common forms.

MODY should not be confused with latent autoimmune diabetes of adults (LADA) — a form of type 1 DM, with slower progression to insulin dependence in later life.



## **Management of Type 2 DM:**

- NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2009.
- Key points are listed below:

### **Dietary advice:**

- 1) encourage high fibre, low glycaemic index sources of carbohydrates
- 2) include low-fat dairy products and oily fish
- 3) control the intake of foods containing saturated fats and trans fatty acids
- 4) limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- 5) discourage use of foods marketed specifically at people with diabetes
- 6) initial target weight loss in an overweight person is 5-10%

### **HbA1c:**

- The general target for patients is 48 mmol/mol (DCCT = 6.5%).
- HbA1c levels below 48 mmol/mol (DCCT = 6.5%) should not be pursued
- however, individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 2-6 months until stable, then 6 monthly

### **Blood pressure:**

- target is < 140/80 mmHg (or < 130/80 mmHg if EOD is present)
- ACE inhibitors are first-line

**The NICE treatment algorithm has become much more complicated following the introduction of new therapies for type 2 DM. Below is a very selected group of points from the algorithm:**

- 1) NICE still suggest a trial of **lifestyle interventions** first many local protocols now recommend starting **metformin** upon diagnosis
- 2) Usually **metformin** is first-line, followed by a **sulfonylurea** if the HbA1c remains > 48 mmol/mol (DCCT = 6.5%)
- 3) if the patient is at risk from hypoglycaemia (or the consequences of) then a **DPP-4 inhibitor (gliptin)** or **thiazolidinedione** should be considered rather than a sulfonylurea
- 4) **Meglitinides** (insulin secretagogues) should be considered for patients with an erratic lifestyle  
(Meglitinides stimulate insulin release and are particularly useful for post-prandial hyperglycaemia or an erratic eating schedule, as patients take them shortly before meals. e.g. Nateglinide, Repaglinide{Novonorm}).
- 5) if HbA1c > 58 mmol/mol (DCCT = 7.5%) then **consider human insulin**
- 6) **metformin** treatment should be **continued** after starting insulin
- 7) **Exenatide:**
  - ✓ Should be used only when insulin would otherwise be started, obesity is a problem (BMI > 35 kg/m<sup>2</sup>) and the need for high dose insulin is likely.
  - ✓ Continue only if beneficial response occurs and is maintained (> 1.0 percentage point HbA1c reduction and weight loss > 3% at 6 months)



### Starting insulin:

- Usually commenced if HbA1c > 58 mmol/mol (DCCT = 7.5%)
- NICE recommend starting with human NPH insulin (isophane, intermediate acting) taken at bed-time or twice daily according to need

### Insulin therapy side-effects

#### 1) Hypoglycaemia

- patients should be taught the signs of hypoglycaemia: sweating, anxiety, blurred vision, confusion, aggression
- conscious patients should take 10-20g of a short-acting carbohydrate (e.g. a glass of Lucozade or non-diet drink, three or more glucose tablets, glucose gel)
- every person treated with insulin should have a **glucagon kit** for emergencies where the patient is not able to orally ingest a short-acting carbohydrate
- Patients who have frequent hypoglycaemic episodes may develop reduced awareness. If this develops then allowing glycaemic control to slip for a period of time may restore their awareness
- beta-blockers reduce hypoglycaemic awareness

#### 2) Lipodystrophy

- typically presents as atrophy of the subcutaneous fat
- can be prevented by rotating the injection site

### Other risk factor modification:

#### 1) Aspirin:

- ☒ Current NICE guidelines suggest giving **aspirin** to:
  - All patients > 50 years and
  - To **younger patients** with **other significant risk factors**.
  - However, recent evidence does not support this approach.
- ☒ The 2010 SIGN guidelines do not advocate the use of aspirin for primary prevention in diabetics

#### 2) Statin:

- ☒ Following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin.
- ☒ The first-line statin of choice is atorvastatin 20mg OD

## 1) **Metformin**

- a biguanide used mainly in the treatment of type 2 diabetes mellitus
- It has a number of actions which improves glucose tolerance (see below).
- Unlike sulphonylureas it does not cause hypoglycaemia and weight gain and is therefore first-line, particularly if the patient is overweight.
- Metformin is also used in PCO and non-alcoholic fatty liver disease

### **Mechanism of action:**

- 1) increases insulin sensitivity
- 2) decreases hepatic gluconeogenesis
- 3) may also reduce GI absorption of carbohydrates

### **Adverse effects:**

- 1) GIT upsets are common (nausea, anorexia, diarrhoea), intolerable in 20%
- 2) reduced vitamin B12 absorption - rarely a clinical problem
- 3) lactic acidosis with severe liver disease or renal failure

### **Contraindications:**

- 1) **chronic kidney disease:** NICE recommend that:
  - ✓ the dose should be reviewed if the creatinine is  $> 130 \mu\text{mol/l}$  (or  $\text{eGFR} < 45 \text{ ml/min}$ ) and
  - ✓ stopped if the creatinine is  $> 150 \mu\text{mol/l}$  (or  $\text{eGFR} < 30 \text{ ml/min}$ )
- 2) Metformin may cause lactic acidosis if taken during a period where there is tissue hypoxia. Examples include:
  - ✓ a recent myocardial infarction,
  - ✓ sepsis,
  - ✓ acute kidney injury and
  - ✓ severe dehydration
- 3) **iodine-containing x-ray contrast media:** examples include:
  - 1) Peripheral arterial angiography,
  - 2) coronary angiography,
  - 3) intravenous pyelography (IVP);
  - ⇒ there is an increasing risk of provoking renal impairment due to contrast nephropathy;
  - ⇒ metformin should be discontinued **on the day of the procedure and for 48 hours thereafter**
- 4) **alcohol abuse** is a relative contraindication

\*it is now increasingly recognised that lactic acidosis secondary to metformin is rare, although it remains important in the context of exams

\*\*metformin is now sometimes used in pregnancy, for example in women with polycystic ovarian syndrome

## 2) Sulfonylureas

- Sulfonylureas are oral hypoglycaemic drugs used in the management of type 2 DM.
- They work by increasing pancreatic insulin secretion and hence are only effective if functional B-cells are present.
- On a molecular level they bind to an ATP-dependent  $K^+$  ( $K_{ATP}$ ) channel on the cell membrane of pancreatic beta cells.

### Common adverse effects:

- 1) Hypoglycaemic episodes (more common with long acting preparations such as chlorpropamide)
- 2) Weight gain

### Rarer adverse effects:

- 1) syndrome of inappropriate ADH secretion (SIADH)
- 2) bone marrow suppression
- 3) liver damage (cholestatic)
- 4) photosensitivity
- 5) peripheral neuropathy

✚ Sulfonylureas should be avoided in breast feeding and pregnancy

## 3) Meglitinides

E.g. **repaglinide** (NovoNorm), **nateglinide**

- insulin secretagogues like sulfonylureas they bind to an ATP-dependent  $K^+$  ( $K_{ATP}$ ) channel on the cell membrane of pancreatic beta cells
- often used for patients with an erratic lifestyle, particularly useful for post-prandial hyperglycaemia or an erratic eating schedule, as patients take them shortly before meals
- adverse effects include **weight gain** and **hypoglycaemia** (less so than sulfonylureas)

## 4) Thiazolidinediones:

- They are **agonists to the PPAR-gamma receptor** and
- **reduce peripheral insulin resistance**
- The PPAR-gamma receptor is an intracellular nuclear receptor. Its natural ligands are free fatty acids and it is thought to control adipocyte differentiation and function.
- pioglitazone is now the only thiazolidinedione on the market
- Rosiglitazone (avandia) was withdrawn in 2010 following concerns about the CV side effect.

### Adverse effects:

- 1) liver impairment: monitor LFTs
- 2) weight gain
- 3) Fluid retention:
  - ✓ Therefore contraindicated in **heart failure**.
  - ✓ The risk of fluid retention is increased if the patient also takes insulin.
- 4) recent studies have indicated an **increased risk of fractures**
- 5) Recent studies showed **increased risk of bladder cancer** in patients taking pioglitazone (HR 2.64)  
NICE guidance on thiazolidinediones
  - only continue if there is a reduction of > 0.5 percentage points in HbA1c in 6 months

## 5) GLP-1 and the new drugs:

- GLP-1(glucagon-like peptide-1), a hormone released by the small intestine in response to an oral glucose load.
- In normal physiology an oral glucose load results in a greater release of insulin than if the same load is given intravenously - this known as the **incretin effect**.
- This effect is largely mediated by GLP-1 and is known to be **decreased in T2DM**.
- Increasing GLP-1 levels is therefore the target of two recent classes of drug, either by:
  - a) An analogue (glucagon-like peptide-1, **GLP-1 mimetics**, e.g. **exenatide**) or
  - b) **Inhibiting its breakdown** (dipeptidyl peptidase-4, **DPP-4 inhibitors** - **the gliptins**).

### **A) Glucagon-like peptide-1 (GLP-1) mimetics (e.g. exenatide)**

- These drugs:
  - ✓ increase insulin secretion and
  - ✓ Inhibit glucagon secretion.

One of the major advances of GLP-1 mimetics is that they typically result in weight loss, in contrast to many medications such as insulin, sulfonylureas, Meglitinides and thiazolidinediones.

- **Exenatide** must be given by **subcutaneous injection** within **60 minutes before the morning and evening meals**. It should not be given after a meal.
- **Liraglutide**
  - ✓ It is the other GLP-1 mimetic currently available.
  - ✓ The main advantages of liraglutide over exenatide is that it only needs to be given **once a day**
- Both exenatide and liraglutide may be combined with metformin and a sulfonylurea.
- Standard release exenatide is also licensed to be used with basal insulin alone or with metformin.

### **NICE state the following:**

- Consider adding exenatide to metformin and a sulfonylurea if:
  - BMI  $\geq 35 \text{ kg/m}^2$  in people of European descent and there are problems associated with high weight, or
  - BMI  $< 35 \text{ kg/m}^2$  and insulin is unacceptable because of occupational implications or weight loss would benefit other comorbidities.
- NICE like patients to have achieved a 1% reduction in HbA1c and 3% weight loss after 6 months to justify the ongoing prescription of GLP-1 mimetics.

### **Adverse Effects:**

- The major adverse effect of GLP-1 mimetics is **nausea and vomiting**.
- The Medicines and Healthcare products Regulatory Agency has issued specific warnings on the use of exenatide, reporting that it has been linked to **severe pancreatitis** and **renal impairment** in some patients.(increases TG)



## **B) Dipeptidyl peptidase-4 (DPP-4) inhibitors:**

**(e.g. Vildagliptin, Sitagliptin, Saxagliptin)**

- 1) oral preparation
- 2) Inhibits breakdown of Glucagon Like peptide - 1.
- 3) trials to date show that the drugs are relatively well tolerated with no increased incidence of hypoglycaemia
- 4) do not cause weight gain

### **NICE guidelines on DPP-4 inhibitors:**

continue DPP-4 inhibitor only if there is a reduction of > 0.5 percentage points in HBA1c in 6 months (as thiazolidinedione)

- NICE suggest that a DPP-4 inhibitor might be preferable to a thiazolidinedione if further weight gain would cause significant problems, a thiazolidinedione is contraindicated or the person has had a poor response to a thiazolidinedione



## **6) Sodium-glucose cotransporter 2 (SGLT2) inhibitor:**

### **Canagliflozin & dapagliflozin**

- It can be given as second line agent with metformin if a sulfonylurea is contraindicated or not tolerated.
- It can also be given as a third agent in addition to metformin and a sulfonylurea or thiazolidinediones.
- **The reported side effects of this drug are:**
  - 1) hypoglycaemia when used in combination with insulin or a sulfonylurea,
  - 2) vaginal candidiasis, urinary tract infection,
  - 3) polyuria and urinary frequency.

## **Diabetes mellitus in Ramadan**

- Clearly it is a personal decision whether a patient decides to fast.
- It may however be worthwhile exploring the fact that people with chronic conditions are exempt from fasting or may be able to delay fasting to the shorter days of the winter months.
- It is however known that many Muslim patients with diabetes do not class themselves as having a chronic/serious condition which should exempt them from fasting.
- Around 79% of Muslim patients with type 2 diabetes mellitus fast Ramadan<sup>2</sup>. There is an excellent patient information leaflet from Diabetes UK and the Muslim Council of Britain which explores these options in more detail.

- **If a patient with type 2 diabetes mellitus does decide to fast:**

- a) they should eat a meal containing long-acting carbohydrates prior to sunrise (Suhoor)
- b) patients should be given a blood glucose monitor to allow them to check their glucose levels, particularly if they feel unwell
- c) for patients taking metformin the expert consensus is that the dose should be split one-third before sunrise (Suhoor) and two-thirds after sunset (Iftar)
- d) Expert consensus also recommends switching once-daily sulfonylureas to after sunset.
- e) For patients taking twice-daily preparations such as gliclazide (Diamicron) it is recommended that a larger proportion of the dose is taken after sunset.
- f) no adjustment is needed for patients taking pioglitazone

1. Management of people with diabetes wanting to fast during Ramadan BMJ 2010;340:c3053

2. Salti I et al. Results of the Epidemiology of Diabetes and Ramadan (EPIDIAR) study. Diabetes Care 2004;27:2306-11.



# **Diabetes mellitus in Pregnancy**

- Diabetes mellitus may be a pre-existing problem or develop during pregnancy, gestational diabetes.
- It complicates around 1 in 40 pregnancies. NICE updated the guidance in 2015

## **Risk factors for gestational diabetes:**

- 1) BMI of  $> 30 \text{ kg/m}^2$
- 2) Previous macrosomic baby weighing 4.5 kg or above.
- 3) previous gestational diabetes
- 4) first-degree relative with diabetes
- 5) family origin with a high prevalence of DM (South Asian, black Caribbean and Middle Eastern)

## **Screening for gestational diabetes:**

- 1) if a woman has had gestational diabetes previously an (OGTT) should be performed:
  - ✓ as soon as possible after booking and
  - ✓ at 24 - 28 weeks if the first test is normal

NICE also recommend that early self-monitoring of blood glucose is an alternative to the OGTTs

- 2) women with any of the other risk factors should be offered an OGTT at 24-28 weeks

## **Diagnostic thresholds for gestational diabetes**

These have recently been updated by NICE, gestational diabetes is diagnosed if either:

- ⇒ fasting glucose is  $\geq 5.6 \text{ mmol/l}$
- ⇒ 2-hour glucose is  $\geq 7.8 \text{ mmol/l}$

## **Management of gestational diabetes:**

- 1) newly diagnosed women should be seen in a joint diabetes and antenatal clinic within a week
- 2) women should be taught about selfmonitoring of blood glucose
- 3) advice about diet (including eating foods with a low glycaemic index) and exercise should be given
- 4) if the fasting plasma glucose level is  $< 7 \text{ mmol/l}$ 
  - ⇒ a trial of diet and exercise should be offered
  - ⇒ if glucose targets are not met within 1-2 weeks of altering diet/exercise metformin should be started
  - ⇒ if glucose targets are still not met insulin should be added to diet/exercise/metformin
- 5) if at the time of diagnosis the fasting glucose level is  $\geq 7 \text{ mmol/l}$ 
  - ⇒ insulin should be started
- 6) if the plasma glucose level is between  $6-6.9 \text{ mmol/l}$  and there is evidence of complications such as macrosomia or hydramnios,
  - ⇒ insulin should be offered
- 7) glibenclamide should only be offered for women who cannot tolerate metformin or those who fail to meet the glucose targets with metformin but decline insulin treatment

### **Management of pre-existing diabetes**

- 1) **weight loss** for women with BMI of  $> 27 \text{ kg/m}^2$
- 2) stop oral hypoglycaemic agents, **apart from metformin**, and **commence insulin**
- 3) **folic acid 5 mg/day** from pre-conception to 12 weeks gestation
- 4) **detailed anomaly scan** at 20 weeks including four-chamber view of the heart and outflow tracts
- 5) **tight glycaemic control** reduces complication rates
- 6) **treat retinopathy** as can worsen during pregnancy

### **Targets for self monitoring of pregnant women** (pre-existing and gestational diabetes)

| Time               | Target          |
|--------------------|-----------------|
| Fasting            | 5.3 mmol/l      |
| 1 hour after meals | 7.8 mmol/l, or: |
| 2 hour after meals | 6.4 mmol/l      |



# **Diabetic ketoacidosis**

**The most common precipitating factors of diabetic ketoacidosis (DKA) are:**

- ✓ infection,
- ✓ missed insulin doses and
- ✓ myocardial infarction

**American Diabetes Association diagnostic criteria are as follows:**

- 1) blood glucose >13.8 mmol/l (250)
- 2) pH < 7.30
- 3) serum bicarbonate <18 mmol/l
- 4) anion gap > 10
- 5) ketonaemia (ketones >3 mmol/l)

**Management:**

- 1) **Fluid replacement:** most patients with DKA are deplete around **5-8 litres**. Isotonic saline is used initially
- 2) **Insulin:** an intravenous infusion should be started at **0.1 unit/kg/hour**
- 3) **Once blood glucose is < 15mmol/l (270)** an **infusion of 5% dextrose** should be started
- 4) **correction of hypokalaemia**

**Complications of DKA and its treatment:**

- 1) gastric stasis
- 2) cerebral oedema
- 3) thromboembolism
- 4) acute respiratory distress syndrome ARDS
- 5) acute renal failure AKI

# **Hyperosmolar Hyperglycaemic State**

**Hyperosmolar hyperglycaemic state (HHS) is confirmed by:**

- 1) Dehydration
- 2) Osmolality  $>320\text{mosmol/kg}$
- 3) Hyperglycaemia  $>30\text{ mmol/L}$  (540) with
- 4)  $\text{pH} >7.3$ ,
- 5) bicarbonate  $>15\text{mmol/L}$  and
- 6) no significant ketonuria  $<3\text{mmol/L}$

HHS typically occurs in the elderly and is often a first presentation of Type 2 Diabetes Mellitus.

Using the blood results, osmolality can be calculated with the formula  $2(\text{Na}+\text{K}) + \text{glucose} + \text{urea}$

**Goals of treatment includes:**

- 1) Normalise the osmolality
  - 2) Replace fluid and electrolyte losses
  - 3) Normalise blood glucose
  - 4) Prevention of complications: Arterial or venous thrombosis/cerebral oedema
- Fluid replacement must commence first; an initial insulin bolus of 0.15 U per kg may be given once infusions are underway.
  - Fluid replacement alone with 0.9% sodium chloride solution will result in falling blood glucose.
  - Insulin treatment prior to adequate fluid replacement may result in **cardiovascular collapse** as water moves out of the intravascular space, with a resulting decline in intravascular volume.
  - Patients with HHS are often exquisitely sensitive to insulin and require much lower doses than in diabetic ketoacidosis (DKA).
  - The recommended insulin dose is:
    - ⇒ a fixed rate intravenous insulin infusion (FRII) given at **0.05 units per kg per hour** (e.g. 4 units/hr in an 80 kg man) is used
  - Beware of rapid correction of hyponatraemia, may lead to **cerebral pontine myelinolysis**

## **Diabetic neuropathy**

NICE updated its guidance on the management of neuropathic pain in 2013. Diabetic neuropathy is now managed in the same way as other forms of neuropathic pain:

- first-line treatment: amitriptyline, duloxetine, gabapentin or pregabalin
- if the first-line drug treatment does not work try one of the other 3 drugs
- tramadol may be used as 'rescue therapy' for exacerbations of neuropathic pain
- topical capsaicin may be used for localised neuropathic pain (e.g. post-herpetic neuralgia)
- pain management clinics may be useful in patients with resistant problems

## **Gastroparesis**

- symptoms include erratic blood glucose control, bloating and vomiting
- management options include metoclopramide, domperidone or erythromycin (prokinetic agents)

## **Diabetic nephropathy:**

### **Screening:**

- all patients should be screened annually
- albumin: creatinine ratio (ACR) in early morning specimen
- ACR > 2.5 in male = microalbuminuria  
> 3.5 in female

### **Management:**

- 1) dietary protein restriction
- 2) tight glycaemic control
- 3) BP control: aim for < 130/80 mmHg
- 4) Benefits independent of blood pressure control have been demonstrated for ACE inhibitors (ACE-i) and angiotensin II receptor blockers (A2RB).
- 5) Combinations of ACE-i and A2RB are not commonly used anymore following the ON-TARGET trial which showed **worse outcomes for patients on dual blockade**
- 6) control dyslipidaemia e.g. Statins

# Diabetic Retinopathy

- Diabetic retinopathy is the most common cause of blindness in adults aged 35-65 years-old.
- Hyperglycaemia is thought to cause increased retinal blood flow and abnormal metabolism in the retinal vessel walls.
- This precipitates damage to endothelial cells and pericytes.
- **Endothelial dysfunction leads to increased vascular permeability** which causes the characteristic **exudates** seen on fundoscopy.
- **Pericyte dysfunction** predisposes to the formation of **microaneurysms**.
- **Neovascularization** is thought to be caused by the production of **growth factors** in response to **retinal ischaemia**.
- In exams you are most likely to be asked about the characteristic features of the various stages/types of diabetic retinopathy.
- Recently a new classification system has been proposed, dividing patients into those with non-proliferative diabetic retinopathy (NPDR) and those with proliferative retinopathy (PDR):

| Traditional classification                                                                                                                                                                                                                                                                                                                       | New classification                                                                                                                                                                                                                                                                         |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Background retinopathy:</b> <ol style="list-style-type: none"> <li>1) microaneurysms (dots)</li> <li>2) blot haemorrhages (<math>\leq 3</math>)</li> <li>3) hard exudates</li> </ol>                                                                                                                                                          | <b>Mild NPDR</b> <ul style="list-style-type: none"> <li>• 1 or more microaneurysm</li> </ul>                                                                                                                                                                                               |
| <b>Pre-proliferative retinopathy:</b> <ol style="list-style-type: none"> <li>1) cotton wool spots (soft exudates; ischaemic nerve fibres)</li> <li>2) <math>&gt; 3</math> blot haemorrhages</li> <li>3) venous beading/looping</li> <li>4) deep/dark cluster haemorrhages more common in Type I DM, treat with laser photocoagulation</li> </ol> | <b>Moderate NPDR</b> <ol style="list-style-type: none"> <li>1) microaneurysms</li> <li>2) blot haemorrhages</li> <li>3) hard exudates</li> <li>4) cotton wool spots, venous beading/looping and intraretinal microvascular abnormalities (IRMA) less severe than in severe NPDR</li> </ol> |
|                                                                                                                                                                                                                                                                                                                                                  | <b>Severe NPDR</b> <ol style="list-style-type: none"> <li>1) blot haemorrhages and microaneurysms in 4 quadrants</li> <li>2) venous beading in at least 2 quadrants</li> <li>3) IRMA in at least 1 quadrant</li> </ol>                                                                     |

## Proliferative retinopathy:

- 1) retinal neovascularisation - may lead to vitreous haemorrhage
- 2) fibrous tissue forming anterior to retinal disc
- 3) more common in Type I DM, 50% blind in 5 years

## Maculopathy:

- 1) based on location rather than severity, anything is potentially serious
- 2) hard exudates and other 'background' changes on macula
- 3) check visual acuity
- 4) more common in Type II DM

## **DVLA: diabetes mellitus:**

- Until recently people with diabetes who used insulin could not hold a HGV (heavy goods vehicle) licence.
- The DVLA changed the rules in October 2011.
- The following standards need to be met (and also apply to patients using other hypoglycaemic inducing drugs such as sulfonylureas):
  - 1) there has not been any severe hypoglycaemic event in the previous 12 months
  - 2) the driver must show adequate control of the condition by regular blood glucose monitoring\*, at least twice daily and at times relevant to driving
  - 3) the driver has full hypoglycaemic awareness
  - 4) the driver must demonstrate an understanding of the risks of hypoglycaemia
  - 5) There are no other debarring complications of diabetes

**From a practical point of view patients on insulin who want to apply for a Group 2 (HGV) licence need to complete a D2 form**

They may also be required to produce a D4 Medical examination report

### **Other specific points for group 1 drivers:**

- 1) If on insulin then patient can drive a car as long as they have hypoglycaemic awareness, not more than one episode of hypoglycaemia requiring the assistance of another person within the preceding 12 months and no relevant visual impairment. Drivers are normally contacted by DVLA
- 2) If on tablets or exenatide no need to notify DVLA. If tablets may induce hypoglycaemia (e.g. sulfonylureas) then there must not have been more than one episode of hypoglycaemia requiring the assistance of another person within the preceding 12 months
- 3) if diet controlled alone then no requirement to inform DVLA

\*to demonstrate adequate control, the Secretary of State's Honorary Medical Advisory Panel on Diabetes Mellitus has recommended that applicants will need to have used blood glucose meters with a memory function to measure and record blood glucose levels for at least 3 months prior to submitting their application

## **Glucagonoma**

- Presented with **abdominal pain**, **watery diarrhea** extensive rash (**necrolytic migratory erythema**)
- **Other features of glucagonoma include:**
  - 1) **Diabetes mellitus**
  - 2) Hypoaminoacidaemia
  - 3) Cheilosis
  - 4) Normochromic normocytic anaemia
  - 5) Venous thrombosis
  - 6) Neuropsychiatric features.
- At least 50% are metastatic at presentation, so prognosis is poor.

# **Hypoglycaemia**

## **Causes:**

- 1) insulinoma - increased ratio of proinsulin to insulin
- 2) self-administration of insulin/sulphonylureas
- 3) liver failure
- 4) Addison's disease
- 5) alcohol

## **Other possible causes in children:**

- **nesidioblastosis** - beta cell hyperplasia

# **Insulinoma**

- An insulinoma is a neuroendocrine tumour
- deriving mainly from pancreatic Islets of Langerhans cells
- most common pancreatic endocrine tumour
- 10% malignant, 10% multiple
- of patients with multiple tumours, 50% have MEN-1

## **Features:**

- 1) hypoglycaemia: typically early in morning or just before meal, e.g. diplopia, weakness etc
- 2) rapid weight gain may be seen
- 3) high insulin, raised proinsulin: insulin ratio
- 4) high C-peptide

## **Diagnosis:**

- 1) supervised, prolonged fasting (up to 72 hours)
- 2) CT pancreas

## **Management:**

- 1) **surgery**
- 2) **diazoxide** and **somatostatin** if patients are not candidates for surgery

# **Calcium Metabolism**

- **The two hormones which primarily control calcium metabolism are:**
  - 1) parathyroid hormone (PTH)
  - 2) 1,25-dihydroxycholecalciferol (calcitriol, the active form of vitamin D)
- **Other hormones include:**
  - 1) calcitonin: secreted from the parafollicular cells (C-cells) of the thyroid gland
  - 2) thyroxine
  - 3) growth hormone

## **Actions of parathyroid hormone:**

Increases plasma calcium, decreases plasma phosphate

- 1) increases renal tubular reabsorption of calcium
- 2) decreases renal phosphate reabsorption
- 3) increases renal conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol
- 4) increases osteoclastic activity

## **Actions of 1, 25-dihydroxycholecalciferol:**

Increases plasma calcium and plasma phosphate

- 1) increases renal tubular reabsorption and gut absorption of calcium
- 2) increases renal phosphate reabsorption
- 3) increases osteoclastic activity

# Hypercalcaemia

## Causes:

The most common causes of hypercalcaemia are:

- 1) **malignancy:**
  - ✓ bone metastases,
  - ✓ myeloma,
  - ✓ PTHrP from squamous cell lung cancer

- 2) **primary hyperparathyroidism**

## **Other causes include:**

- 1) sarcoidosis (other granulomas may lead to hypercalcaemia e.g. TB and histoplasmosis)
- 2) vitamin D intoxication
- 3) acromegaly
- 4) thyrotoxicosis
- 5) Addison's disease
- 6) Milk-alkali syndrome
- 7) drugs: thiazides, calcium containing antacids
- 8) dehydration
- 9) Paget's disease (usually normal but hypercalcaemia may occur with prolonged immobilization).

(most common): Malignancy, 1ry hyperPTH,.....

(Hormones):---->vit D excess, granuloma, Acromegaly, Thyrotoxicosis, Addison,

(intake)----->: Milk- Alkali S, dehydration, drugs.....

(others)----->Paget D (prolonged immobilization)

## Hypercalcaemia management:

- 1) The initial management of hypercalcaemia is:
  - Rehydration with normal saline, typically 3-4 litres/day.
  - Following rehydration bisphosphonates may be used. They typically take 2-3 days to work with maximal effect being seen at 7 days
- 2) Other options include:
  - Calcitonin - quicker effect than bisphosphonates
  - steroids in sarcoidosis
  - There is a limited role for the use of furosemide in hypercalcaemia. It may be useful in patients who cannot tolerate aggressive fluid rehydration

## **Familial hypocalciuric hypercalcaemia (FHH)**

- a benign cause of hypercalcaemia- it is not associated with any specific abnormality and requires no treatment
- **Autosomal dominant** with high penetrance.
- Affected heterozygous patients typically present in childhood with the incidental discovery of:
  - 1) mild hypercalcemia
  - 2) hypocalciuria
  - 3) a normal PTH level, and
  - 4) High-normal to frankly elevated serum Mg levels.



# Primary hyperparathyroidism

- In exams primary hyperparathyroidism is stereotypically seen in **elderly females** with an unquenchable **thirst** and an **inappropriately normal** or **raised PTH** level.
- It is most commonly due to a **solitary adenoma**

## Causes of primary hyperparathyroidism:

- 80%: solitary adenoma
- 15%: hyperplasia
- 4%: multiple adenoma
- **1%: carcinoma** (rare but grossly elevated PTH)

## Features: - 'bones, stones, abdominal groan and psychic moans'

- 1) polydipsia, polyuria
- 2) hypertension
- 3) peptic ulceration/constipation/pancreatitis
- 4) bone pain/fracture
- 5) renal stones
- 6) depression

## Associations:

- hypertension
- multiple endocrine neoplasia: MEN I and II

## Investigations:

- 1) raised calcium, low phosphate
- 2) PTH may be **raised** or **inappropriately normal**
- 3) technetium-MIBI subtraction scan

## Management: Surgery



Bilateral hand radiographs in a middle-aged woman demonstrating generalised osteopenia, erosion of the terminal phalangeal tufts (acro-osteolysis) and sub-periosteal resorption of bone particularly the radial aspects of the 2nd and 3rd middle phalanges. These changes are consistent with a diagnosis of hyperparathyroidism.

groans: تأوهات.....unquenchable: عدم الرى....من الارتواء (MIBI or sesta-mibi scan). Technetium (99mTc) sestamibi : is a pharmaceutical AGENT used in nuclear medicine imaging; complex consisting of the radioisotope technetium-99m bound to six (sesta=6) methoxy-isobutyl-isonitrile (MIBI)ligands. The anion is not defined. A scan of a patient using MIBI is commonly known as a 'MIBI scan.'

# **Hypocalcaemia**

As extracellular calcium concentrations are important for muscle and nerve function many of the features seen in hypocalcaemia are a result of neuromuscular excitability

## **Features:**

- 1) tetany: muscle twitching, cramping and spasm
- 2) perioral paraesthesia
- 3) if chronic: depression, cataracts
- 4) ECG: prolonged QT interval

## **Trousseau's sign:**

- carpal spasm if the brachial artery occluded by inflating the blood pressure cuff and maintaining pressure above systolic
- wrist flexion and fingers drawn together
- seen in around 95% of patients with hypocalcaemia and around 1% of normocalcaemic people

## **Chvostek's sign:**

- tapping over parotid causes facial muscles to twitch
- seen in around 70% of patients with hypocalcaemia and around 10% of normocalcaemic people

## **Causes and management:**

The clinical history combined with parathyroid hormone levels will reveal the cause of hypocalcaemia in the majority of cases

## **Causes:**

- 1) vitamin D deficiency (osteomalacia)
- 2) chronic renal failure
- 3) hypoparathyroidism (e.g. post thyroid/parathyroid surgery)
- 4) pseudohypoparathyroidism (target cells insensitive to PTH)
- 5) magnesium deficiency (due to end organ PTH resistance)
- 6) rhabdomyolysis (initial stages)
- 7) Acute pancreatitis may also cause hypocalcaemia.
- 8) massive blood transfusion
- 9) Contamination of blood samples with EDTA may also give falsely low calcium levels

## **Management:**

- 1) Acute management of severe hypocalcaemia is with intravenous replacement. The preferred method is with intravenous calcium gluconate, 10ml of 10% solution over 10 minutes
- 2) intravenous calcium chloride is more likely to cause **local irritation**
- 3) ECG monitoring is recommended
- 4) further management depends on the underlying cause

# Hypoparathyroidism

## Primary hypoparathyroidism:

- Decrease PTH secretion. e.g. secondary to thyroid surgery\*
- low calcium, high phosphate, low PTH
- treated with alfacalcidol

\*this may seem an oxymoron متناقض, but most medical textbooks classify hypoparathyroidism which is secondary to surgery as being 'primary hypoparathyroidism'

The main symptoms of hypoparathyroidism are secondary to hypocalcaemia: see above

## Pseudohypoparathyroidism

- typically inherited in an **autosomal dominant** fashion
- target cells being insensitive to PTH due to a mutation in a G protein
- low calcium, high phosphate, high PTH

### Features:

- 1) short stature , obesity, round face
- 2) Short fourth and fifth metacarpals,
- 3) **Slipped femoral epiphysis is a recognized feature**
- 4) Cognitive impairment, Low IQ.

**Type I:** there is a complete receptor defect.

#### Type 1a:

- ☒ Albrights Hereditary Osteodystrophy
- ☒ biochemistry abnormality in combination of these clinical features

Type 1b would have the same biochemistry but lack the clinical features.

**Type II:** the cell receptor is intact.

**Diagnosis:** by measuring **urinary cAMP** and **phosphate levels** following **infusion of PTH**

- 1) **In hypoparathyroidism** this will cause an **increase in both cAMP and phosphate levels.**
- 2) **In pseudohypoparathyroidism type I** **neither cAMP nor phosphate levels are increased**
- 3) **In pseudohypoparathyroidism type II** **only cAMP rises.**

## Pseudo-pseudo-hypoparathyroidism:

- **similar phenotype** (skeletal defects) to pseudohypoparathyroidism but **normal biochemistry** (normal ---- > calcium, phosphate & PTH)

## **DiGeorge syndrome:**

- DiGeorge syndrome is a primary immunodeficiency disorder
- Caused by T-cell deficiency and dysfunction.
- It is an example of a microdeletion syndrome

### **Features:**

- 1) at risk of **viral** and **fungal** infections
- 2) parathyroid gland hypoplasia → **hypocalcaemic tetany**
- 3) thymus hypoplasia
- 4) T-lymphocyte deficiency/dysfunction

## **Hungry bone syndrome**

- An uncommon entity but can occur after parathyroidectomy if the hyperparathyroidism has been long standing.
- The mechanism is thought to be thus: high pre-operative levels of parathyroid hormone provide a constant stimulus for osteoclast activity creating the hypercalcaemic state by de-mineralizing the bones.
- This process can result in x-ray changes very similar to metastatic lytic lesions if left untreated.
- Upon removal of the parathyroid adenoma the hormone levels fall rapidly (they have a very short half life) and the osteoclast activity is subsequently diminished and the bones rapidly begin re-mineralisation - 'hungry bone syndrome'.
- This process can be uncomfortable and also result in systemic hypocalcaemia.

# Metabolic syndrome

- Unfortunately there are a number of competing definitions of metabolic syndrome at present time.
- It is thought that the key pathophysiological factor is insulin resistance.
- SIGN recommend using criteria similar to those from the **American Heart Association**. The similarity of the International Diabetes Federation criteria should be noted.
- For a diagnosis of metabolic syndrome at least 3 of the following should be identified:**
  - elevated waist circumference:  
Men > 102 cm,  
Women > 88 cm
  - elevated triglycerides: > 1.7 mmol/L
  - reduced HDL:  
< 1.03 mmol/L in males and  
< 1.29 mmol/L in females
  - raised blood pressure: > 130/85 mmHg, or active treatment of hypertension
  - raised fasting plasma glucose > 5.6 mmol/L(100) , or previously diagnosed type 2 DM
- The International Diabetes Federation** produced a consensus set of diagnostic criteria in 2005, which are now widely in use.

These require:

- the presence of central obesity defined as:

Waist circumference > 94cm for Europic men  
And > 80cm for Europic women,  
with ethnicity specific values for other groups)

Plus any two of four factors:

- raised triglycerides level: > 1.7 mmol/L, or specific treatment for this lipid abnormality
- reduced HDL cholesterol: < 1.03 mmol/L in males and < 1.29 mmol/L in females, or specific treatment for this lipid abnormality
- raised blood pressure: > 130/85 mm Hg, or active treatment of hypertension
- raised fasting plasma glucose > 5.6 mmol/L, or previously diagnosed type 2 diabetes

In 1999 the **WHO** produced diagnostic criteria which required:

- the presence of diabetes mellitus, impaired glucose tolerance, impaired fasting glucose or insulin resistance, AND two of the following:
  - blood pressure: > 140/90 mmHg
  - dyslipidaemia: triglycerides: > 1.695 mmol/L and/or high-density lipoprotein cholesterol (HDL-C) < 0.9 mmol/L (male), < 1.0 mmol/L (female)
  - central obesity: waist:hip ratio > 0.90 (male), > 0.85 (female), and/or body mass index > 30 kg/m<sup>2</sup>
  - microalbuminuria: urinary albumin excretion ratio > 20 mg/min or albumin: creatinine ratio > 30 mg/g

Other associated features include:

- raised uric acid levels**
- non-alcoholic fatty liver disease NAFLD**
- polycystic ovarian syndrome PCOS**

# Obesity

- Obesity  $> 30 \text{ kg/m}^2$  - Overweight  $25\text{-}30 \text{ kg/m}^2$

## Leptin

- Leptin is thought to play a key role in the regulation of body weight.
- It is **produced by adipose tissue** and acts on satiety centres in the hypothalamus and **decreases appetite**. More adipose tissue (e.g. in obesity) results in high leptin levels.
- Leptin stimulates the release of melanocyte-stimulating hormone (MSH) and corticotrophin-releasing hormone (CRH).
- Low levels of leptin stimulates the release of neuropeptide Y (NPY)

## Ghrelin

- Whereas leptin induces satiety, **ghrelin stimulates hunger**.
- It is produced mainly by the P/D1 cells lining the fundus of the stomach and epsilon cells of the pancreas.
- Ghrelin levels increase before meals and decrease after meals.

## Obesity: therapeutic options:

The management of obesity consists of a step-wise approach:

- 1) conservative: diet, exercise
- 2) medical
- 3) surgical

## Orlistat:

- It is a **pancreatic lipase inhibitor** used in the management of obesity.
- Adverse effects include **faecal urgency/incontinence and flatulence**.
- A lower dose version is now available without prescription ('Alli').
- NICE have defined criteria for the use of orlistat.  
It should **only be prescribed as part of an overall plan** for managing obesity in adults who have:
  - BMI of  $28 \text{ kg/m}^2$  or more with associated risk factors, or
  - BMI of  $30 \text{ kg/m}^2$  or more
  - continued if weight loss e.g. 5% at 3 months
- Orlistat is normally used for  $< 1$  year

## Sibutramine:

- **withdrawn** January 2010 by the European Medicines Agency due to an increased **risk of cardiovascular events**
- **centrally acting appetite suppressant** (**inhibits uptake of serotonin and noradrenaline at hypothalamic sites that regulate food intake**)
- adverse effects include **hypertension** (monitor blood pressure and pulse during treatment), **dry mouth, anorexia, constipation, headache and insomnia**
- contraindicated in psychiatric illness, hypertension, IHD, arrhythmias and stroke

## Rimonabant:

- **a specific CB1 cannabinoid receptor antagonist,**

- **withdrawn** in October 2008 after the European Medicines Agency warned of serious **psychiatric problems** including **suicide**
- ☒ Anti-obesity drug should be discontinued if weight loss is less than 5% after the first 12 weeks.
- ☒ Combination drug therapy is contraindicated at present and drugs should never be used as the sole element of treatment.
- ☒ Diet and exercise have been shown to be ineffective over the long term.
- ☒ **> 90%** of people who attempt to lose weight **gain it all back**.

### Obesity: Bariatric Surgery:

- The use of bariatric surgery for obesity has developed significantly over the past decade.
- It is now recognized that for many obese patients who fail to lose weight with lifestyle and drug interventions the risks and expense of long-term obesity outweigh those of surgery.

#### NICE bariatric referral cut-offs

- with risk factors (T2DM, BP etc):  $> 35 \text{ kg/m}^2$
- no risk factors:  $> 40 \text{ kg/m}^2$

### NICE guidelines on bariatric surgery for adults:

Consider surgery for people with severe obesity if:

- 1) they have a BMI of:
  - ✓  $40 \text{ kg/m}^2$  or more, or
  - ✓ between  $35 \text{ kg/m}^2$  and  $40 \text{ kg/m}^2$  and other significant disease (for example, type 2 diabetes mellitus, hypertension) that could be improved if they lost weight
- 2) all appropriate non-surgical measures have failed to achieve or maintain adequate clinically beneficial weight loss for at least 6 months
- 3) they are receiving or will receive intensive specialist management
- 4) they are generally fit for anaesthesia and surgery
- 5) they commit to the need for long-term follow-up

Consider surgery as a **first-line option** for adults with a **BMI of more than  $50 \text{ kg/m}^2$**  in whom surgical intervention is considered appropriate;  
Consider orlistat before surgery if the waiting time is long

## Types of bariatric surgery:

### 1) primarily restrictive:

- ☒ Laparoscopic-adjustable **gastric banding** (LAGB) or
- ☒ **sleeve gastrectomy**

### 2) primarily malabsorptive:

- ☒ **Classic biliopancreatic diversion** (BPD) has now largely been replaced by
- ☒ **biliopancreatic diversion with duodenal switch** (potent & rapid Wt loss)

### 3) mixed: **Roux-en-Y gastric bypass** surgery

## Which operation?

### 1) LAGB produces

- ✓ less weight loss than malabsorptive or mixed procedures
- ✓ but as it has fewer complications it is normally **the first-line intervention** in patients with a BMI of 30-39kg/m<sup>2</sup>

### 2) Patients with a BMI > 40 kg/m<sup>2</sup> May be considered for

- ✓ a gastric bypass or
- ✓ sleeve gastrectomy (may be done as a sole procedure or as an initial procedure prior to bypass)

### 3) primarily malabsorptive procedures

- ⇒ are usually reserved for **very obese patients** (e.g. BMI > 60 kg/m<sup>2</sup>)



## WHO / Fredrickson classification of primary hyperlipidaemias

| Type | Average of overnight serum | Elevated particles | Associated clinical disorders                                                                                              | Serum Total Cholesterol | Serum TG |
|------|----------------------------|--------------------|----------------------------------------------------------------------------------------------------------------------------|-------------------------|----------|
| I    | Creamy top layer           | Chylomicrons       | <ul style="list-style-type: none"> <li>Lipoprotein lipase deficiency,</li> <li>apolipoprotein C-II deficiency</li> </ul>   | N                       | ++       |
| Ila  | Clear                      | LDL                | Familial hypercholesterolemia, polygenic hypercholesterolemia, nephrosis, hypothyroidism, familial combined hyperlipidemia | ++                      | N        |
| Ilb  | Clear                      | LDL, VLDL          | Familial combined hyperlipidemia                                                                                           | ++                      | +        |
| III  | Turbid                     | IDL                | Dysbetalipoproteinemia                                                                                                     | +                       | +        |
| IV   | Turbid                     | VLDL               | Familial hypertriglyceridemia, familial combined hyperlipidemia, sporadic hypertriglyceridemia, diabetes                   | N+                      | ++       |
| V    | Creamy top, turbid bottom  | Chylomicrons, VLDL | Diabetes                                                                                                                   | +                       | ++       |

Note that the WHO classification is simply a biochemical phenotypic classification based on which lipoprotein is raised.

Also the classification was devised before the importance of HDL as a prognostic indicator was recognised.

\* IDL = intermediate-density lipoproteins; LDL = low-density lipoproteins; TC = total cholesterol; TG = triglycerides; VLDL = very low-density lipoproteins;  
 + = increased; ++ = greatly increased; N= normal; N+ = normal or increased

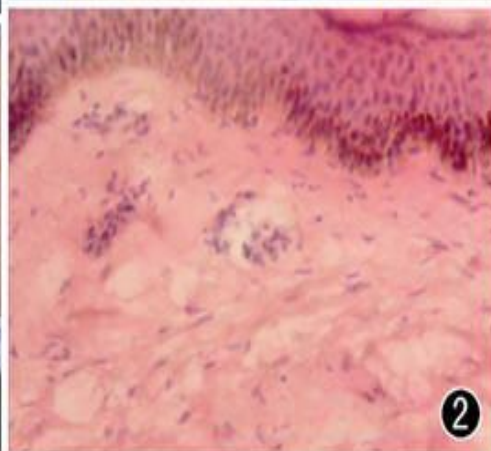
## **Type I hyperlipidaemia:**

- recessive inheritance
- hyperchylomicronaemia
- normal serum cholesterol
- increased triglyceride primarily in chylomicrons
- Apo-CII deficiency or lipoprotein lipase deficiency
- risk of atherosclerosis is thought to be slight

### **Features include:**

- 1) eruptive xanthomata
- 2) lipaemia retinalis
- 3) acute pancreatitis

Note that this classification as a type I hyperlipidaemia is a biochemical one and that a child with type I hyperlipidaemia (hyperchylomicronaemia) may develop a type V hyperlipidaemia (hyperchylomicronaemia and increased VLDL) as an adult.



This milky looking serum sample

## **Type 2A hyperlipidaemia:**

### **Familial Hypercholesterolaemia**

- Autosomal dominant disorder of chromosome 19 causing a mutation in the LDL receptor.
- It results in high levels of LDL-cholesterol which, if untreated, may cause early CVD.
- untreated life expectancy is 20 years
- There are homozygous and heterozygous forms:
  - ⇒ Heterozygosity occurs in 1 in 500 people.
  - ⇒ Homozygosity is rarer and is associated with earlier onset of premature CVD even in childhood.
- It is defined in the WHO classification as a type IIa hyperlipidaemia.

**Clinical diagnosis** is now based on the Simon Broome criteria

#### **The Simon Broome criteria:**

- 1) in adults total cholesterol TC > 7.5 mmol/l and LDL-C > 4.9 mmol/l or  
Children TC > 6.7 mmol/l and LDL-C > 4.0 mmol/l,

Plus:

- 1) For definite FH:
  - ⇒ tendon xanthoma in patients or
  - ⇒ 1st or 2nd degree relatives or
  - ⇒ DNA-based evidence of FH
- 2) For possible FH: family history of myocardial infarction:
  - ⇒ below age 50 years in 2nd degree relative,
  - ⇒ below age 60 in 1st degree relative, or
  - ⇒ a family history of raised cholesterol levels



**Tendon Xanthoma**

### **Management**

- 1) the use of CVD risk estimation using standard tables is not appropriate in FH as they do not accurately reflect the risk of CVD
- 2) referral to a specialist lipid clinic is usually required
- 3) the maximum dose of potent statins are usually required
- 4) First-degree relatives:
  - ⇒ Have a 50% chance of having the disorder and should therefore be offered screening.
  - ⇒ This includes children who should be screened by the age of 10 years if there is one affected parent
- 5) statins should be discontinued in women 3 months before conception due to the risk of congenital defects

## **Type 2B hyperlipidaemia:**

- A mixed hyperlipidaemia: raised plasma cholesterol (raised LDL)
- raised triglyceride (raised VLDL)
- polygenic inheritance
- there is an increased risk of ischaemic heart disease

## **Type III hyperlipidaemia (Remnant Hyperlipidaemia):**

- rare cause of **mixed hyperlipidaemia** (raised cholesterol and triglyceride levels)
- also known as **Fredrickson type III hyperlipidaemia**, broad-beta disease and dysbetalipoproteinaemia
- **Autosomal recessive** with variable penetrance
- associated with **apo-e2 homozygosity**
- high incidence of **IHD** and **PAD**
- Premature cardiovascular disease and pancreatitis.
- thought to be caused by impaired removal of **intermediate density lipoprotein (IDL)** from the circulation by the liver

### **Features:**

- 1) yellow palmar creases
- 2) palmer xanthomas
- 3) tuberous xanthomas

**Management:** **fibrates** are first line treatment



Palmer xanthomas

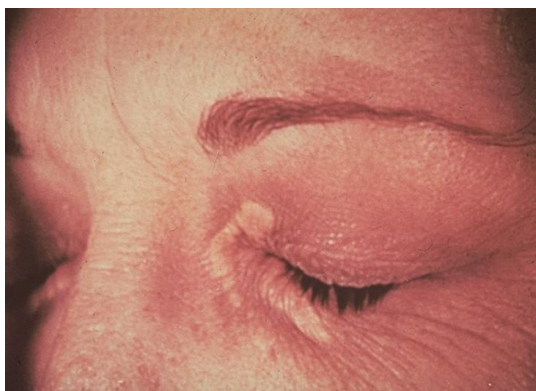


Tuberous xanthomas

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### **Xanthelasma:**

- 1) remnant hyperlipidaemia
- 2) familial hypercholesterolaemia
- 3) Xanthelasma are also seen without lipid abnormalities



Xanthelasma



## Hyperlipidaemia xanthomata:

### A) Eruptive xanthoma

- are due to high TG levels and
- present as multiple red/yellow vesicles on the extensor surfaces (e.g. elbows, knees)

#### Causes of eruptive xanthoma:

Type I hyperlipidaemia



### B) Palmar xanthoma

- 1) remnant hyperlipidaemia (**Type III**)
- 2) may less commonly be seen in familial hypercholesterolaemia (**Type IIa**)



### C) Tuberous xanthoma

remnant hyperlipidaemia (**Type III**)

### D) Tendon xanthoma

- familial hypercholesterolaemia (**Type IIa**)
- Commonly affect the Achilles tendons and the tendons overlying the metacarpophalangeal joints in the hands.
- Less common sites include the extensor hallucis longus and triceps tendons.
- Histologically, the xanthomata consist of accumulations of cholesterol deep within the tendon with fibrous tissue.
- The skin overlying the lesion is usually normal, although if there is inflammation in the tendon, there may be overlying erythema.



Tuberous xanthomas



Tendon Xanthoma

### E) Xanthelasma:

- 1) remnant hyperlipidaemia
- 2) familial hypercholesterolaemia
- 3) Xanthelasma are also seen without lipid abnormalities

#### Management of xanthelasma, options include:

- 1) surgical excision
- 2) topical trichloroacetic acid
- 3) laser therapy
- 4) electrodesiccation

#### Current treatment targets advocate

- ⇒ desirable HDL-C levels > 1 mmol/l and
- ⇒ Plasma TG < 1.7 mmol/l in subjects at risk of CVD.



Xanthelasma

## **Secondary causes of Hyperlipidaemia:**

### **Causes of predominantly hypertriglyceridaemia:**

- 1) Obesity
- 2) Alcohol
- 3) Diabetes mellitus (types 1 and 2)
- 4) Chronic renal failure
- 5) Liver disease
- 6) Drugs: thiazides, non-selective beta-blockers, unopposed oestrogen

### **Causes of predominantly hypercholesterolaemia**

- 1) Nephrotic syndrome
  - 2) Cholestasis
  - 3) Hypothyroidism
- The commonest cause of a mild hypertriglyceridaemia is obesity secondary to a reduced efficacy of lipoprotein lipase activity and overproduction of VLDL.
  - Obesity (BMI above 30) is present in 20% of subjects in the UK, hence why it is the commonest cause of hyperlipidaemia.
  - Alcohol is probably a close second

## **Hyperlipidaemia Management:**

- In 2014 NICE updated their guidelines on lipid modification.
- This proved highly controversial as it meant that we should be recommending statins to a significant proportion of the population over the age of 60 years.
- Anyway, the key points of the new guidelines are summarised below.

### **Primary prevention:**

Who and how to assess risk

- A systematic strategy should be used to identify people aged over 40 years who are likely to be at high risk of cardiovascular disease (CVD), defined as a **10-year risk of 10% or greater**.
- **NICE recommend:**
  - ⇒ Use the QRISK2 CVD risk assessment tool for patients aged  $\leq 84$  years.
  - ⇒ Patients  $\geq 85$  years are at high risk of CVD due to their age.

**QRISK2 should not** be used **in the following situations** as there are more specific guidelines for these patient groups:

- 1) type 1 diabetics
- 2) patients with CKD eGFR  $< 60$  ml/min and/or albuminuria
- 3) patients with a history of familial hyperlipidaemia

**NICE suggest QRISK2 may underestimate CVD risk** in the following population groups:

- 1) people treated for HIV
- 2) people with serious **mental health problems**
- 3) people taking medicines that can cause dyslipidaemia such as **antipsychotics, corticosteroids or immunosuppressant drugs**
- 4) people with **autoimmune disorders/systemic inflammatory disorders** such as **SLE**

### **Measuring lipid levels**

- When measuring lipids:
  - ⇒ Both the total cholesterol and HDL should be checked to provide the most accurate risk of CVD.
  - ⇒ A full lipid profile should also be checked (i.e. including triglycerides) before starting a statin.
  - ⇒ The samples do not need to be fasting.
- In the vast majority of patients the cholesterol measurements will be fed into the QRISK2 tool.
- If however the patient's cholesterol is very high we should consider familial hyperlipidaemia.
- NICE recommend the following that we should **consider the possibility of familial hypercholesterolaemia** and investigate further if:
  - 1) The total cholesterol concentration is  $> 7.5$  mmol/l and **there is a family history of premature coronary heart disease**.
  - 2) Total cholesterol  $> 9.0$  mmol/l or a non-HDL cholesterol (i.e. LDL) of  $> 7.5$  mmol/l **even in the absence of a first-degree family history of premature coronary heart disease**.

### Interpreting the QRISK2 result

- Probably the headline changes in the 2014 guidelines were the new, **lower cut-off of 10-year CVD risk cut-off of 10%**.
- NICE now recommend we offer a statin to people with **a QRISK2 10-year risk of  $\geq 10\%$**
- Lifestyle factors are of course important and NICE recommend that we give patients the option of having their CVD risk reassessed after a period of time before starting a statin.
- **Atorvastatin 20mg** should be offered **first-line**.

### Special situations:

#### 1) **Type 1 diabetes mellitus:**

- NICE recommend that we 'consider statin treatment for the primary prevention of CVD in all adults with type 1 diabetes'
- atorvastatin 20 mg should be offered if type 1 diabetics who are:
  - Older than 40 years, or
  - have had diabetes for more than 10 years or
  - have established nephropathy or
  - have other CVD risk factors

#### 2) **Chronic kidney disease (CKD):**

- atorvastatin 20mg should be offered to patients with CKD
- Increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved and the eGFR  $> 30$  ml/min.
- If the eGFR is  $< 30$  ml/min a renal specialist should be consulted before increasing the dose



## **Secondary prevention**

- All patients with CVD should be taking a statin in the absence of any contraindication.
- Atorvastatin 80mg should be offered first-line.

### **Follow-up of people started on statins:**

- NICE recommend we follow-up patients at 3 months
- repeat a full lipid profile
- if the non-HDL cholesterol has not fallen by at least 40% concordance and lifestyle changes should be discussed with the patient
- NICE recommend we consider increasing the dose of atorvastatin up to 80mg

### **Lifestyle modifications**

These are in many ways predictable but NICE make a number of specific points:

#### **1) Cardioprotective diet:**

- total fat intake should be  $\leq 30\%$  of total energy intake
- saturated fats should be  $\leq 7\%$  of total energy intake
- intake of dietary cholesterol should be  $< 300$  mg/day
- saturated fats should be replaced by monounsaturated and polyunsaturated fats where possible
- replace saturated and monounsaturated fat intake with olive oil, rapeseed oil or spreads based on these oils
- choose wholegrain varieties of starchy food
- reduce their intake of sugar and food products containing refined sugars including fructose
- eat at least 5 portions of fruit and vegetables per day
- eat at least 4 to 5 portions of unsalted nuts, seeds and legumes per week
- eat at least 2 portions of fish per week, including a portion of oily fish

#### **2) Physical activity:**

- each week aim for at least 150 minutes of moderate intensity aerobic activity or 75 minutes of vigorous intensity aerobic activity or a mix of moderate and vigorous aerobic activity
- do muscle strengthening activities on 2 or more days a week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders and arms) in line with national guidance for the general population

#### **3) Weight management:**

- no specific advice is given, overweight patients should be managed in keeping with relevant NICE guidance

#### **4) Alcohol intake:**

- again no specific advice, other than the general recommendation that males drink no more than 3-4 units/day and females no more than 2-3 units/day

#### **5) Smoking cessation:**

- smokers should be encouraged to quit